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U.S. ENVIRONMENTAL PROTECTION AGENCY  
FIFRA SCIENTIFIC ADVISORY PANEL

OPEN MEETING TO CONSIDER AND REVIEW  
SCIENTIFIC ISSUES ASSOCIATED WITH THE  
AGENCY'S ENDOCRINE DISRUPTOR  
SCREENING PROGRAM (EDSP)  
PROPOSED TIER-1 SCREENING BATTERY

EPA CONFERENCE CENTER  
LOBBY LEVEL, ONE POTOMAC YARD  
SOUTH BUILDING  
2777 Crystal Drive  
Arlington, Virginia 22202

MARCH 25, 2008

8:30 A.M.

**U.S. ENVIRONMENTAL PROTECTION AGENCY****FIFRA SCIENTIFIC ADVISORY PANEL****OPEN MEETING TO CONSIDER AND REVIEW****SCIENTIFIC ISSUES ASSOCIATED WITH THE****AGENCY'S ENDOCRINE DISRUPTOR****SCREENING PROGRAM (EDSP)****PROPOSED TIER-1 SCREENING BATTERY****MARCH 25, 2008**

**DR. HEERINGA:** Good morning, everyone.

I'd like to welcome you to the first day of our multiple day session meeting of the FIFRA Science Advisory Panel on the topic of the Endocrine Disrupter Screening Program Proposed Tier 1 Screening Battery. I'm Steve Heeringa of the University of Michigan. I am the current chair of the FIFRA Science Advisory Panel and I'll be chairing this meeting. I'd like to go around the room here, around the table and have the panel members, our panel of experts, introduce themselves to you, give their name, affiliation, a little bit of their background and specific expertise. I'll begin with Dr. Portier.

**DR. PORTIER:** Good morning, I'm Ken Portier, director of statistics at the American Cancer Society National Office in Atlanta. I'm an applied statistician and a member of the permanent panel.

1 **DR. CHAMBERS:** I'm Jan Chambers, I  
2 direct the Center for Environmental Health Sciences at  
3 Mississippi State University. My area of expertise is  
4 pesticide toxicology with emphasis on the pattern of  
5 neurotoxicology and I'm a member of the permanent  
6 panel.

7 **DR. ISOM:** Good morning, I'm Gary Isom  
8 from Purdue University, professor of toxicology. My  
9 area of interest is chemical induced neuro-  
10 degeneration and I am a permanent member of the panel.

11 **DR. BUCHER:** I'm John Bucher, I'm the  
12 Associate Director of the National Toxicology Program.  
13 I'm a toxicologist by training, I have interest in  
14 carcinogenesis and general infusion toxicology and  
15 development of alternative methods.

16 **DR. DELCLOS:** Barry Delclos from the  
17 FDA's National Center of Toxicologic Research in  
18 Arkansas and I have research interest in endocrine  
19 disrupters and carcinogenesis.

20 **DR. ELDRIDGE:** Charles Eldridge, Wake  
21 Forest University, in North Carolina, Department of  
22 Physiology/Pharmacology. Interests are in neuro-  
23 endocrine steroid hormones, reproductive biology.

24 **DR. DENVER:** Good morning, I'm Bob  
25 Denver from the University of Michigan, Ann Arbor and

1 I'm in the Department of Molecular cellular  
2 developmental biology and also ecology and evolutionary  
3 biology and my interests are in developmental neuro  
4 endocrinology, thyroid stearic hormone interaction and  
5 also amphibian metamorphosis.

6 **DR. VANDENBERGH:** I'm John Vandenberg,   
7 I'm a doctor of zoology at NC State University. My  
8 research interests for several years has been on  
9 behavioral endocrinology and its effects upon mostly  
10 female estrogen systems.

11 **DR. LASLEY:** I'm Bill Lasley from the  
12 University of California at Davis at the Center for  
13 Health and the Environment. My interest is in  
14 reproductive toxicology and development of methods used  
15 in population based studies.

16 **DR. COOKE:** Good morning, Gerry Cooke  
17 from Health Canada, in Ottawa, Ontario, Canada and I'm  
18 a reproductive toxicologist with expertise in steroid  
19 genesis, steroid metabolism and gene action.

20 **DR. ZOELLER:** Hi, I'm Tom Zoeller, I'm a  
21 professor of biology at the University of Massachusetts  
22 in Amherst, and my research interests are in thyroid  
23 hormone action, mainly on brain development, on  
24 prenatal brain development.

25 **DR. BROWN:** Terry Brown, from Johns

1 Hopkins University, and the department of biochemistry  
2 and molecular biology. My main areas of interest are  
3 in male reproduction specifically in androgen action  
4 and androgen receptor.

5 **DR. BELCHER:** Good morning. I'm Scott  
6 Belcher, I'm from the University of Cincinnati, the  
7 department of pharmacology, and my primary research  
8 interests are in estrogen receptor signaling and the  
9 role of endocrine disrupters.

10 **DR. KULLMAN:** Good morning. I'm Seth  
11 Kullman from North Carolina State University,  
12 Department of Environmental and Molecular Toxicology.  
13 I'm a molecular toxicologist with an interest in  
14 nuclear receptors and gene inhalation.

15 **DR. HEERINGA:** We have one additional  
16 panel member, David Furlow, who is on his way here from  
17 California we understand, due to a missed flight last  
18 evening, he should be arriving this morning so we'll  
19 have him introduce himself when he has arrived. At  
20 this point in time I'd like to introduce the designated  
21 Federal official for this meeting, Jim Downing.

22 **MR. DOWNING:** Good morning, I'd like to  
23 welcome everybody to this meeting of the FIFRA  
24 Scientific Advisory Panel. I'm Jim Downing, the  
25 designated Federal official for this particular SAP

1 meeting. As you know this is the first day of a  
2 planned four day meeting, on the endocrine disrupter  
3 screening program, EDSP, proposed Tier 1 screening  
4 battery. As the DFO for this meeting I serve as the  
5 liaison between the panel and the Agency and I'm  
6 responsible for insuring that all provisions of the  
7 Federal Advisory Committee Act are met.

8 I want to thank Dr. Heeringa for  
9 introducing the panel and acting as the chair for this  
10 meeting, and I want to thank the members of the panel  
11 and public for attending this meeting today, as well as  
12 all the people from EPA who will be giving  
13 presentations at the meeting. We mentioned briefly the  
14 function of the SAP and a little bit about the panel  
15 composition here today. By way of background, the  
16 FIFRA SAP is a Federal Advisory Committee under the  
17 FACA, F-A-C-A, provides for independent scientific peer  
18 review and advice at the Agency on pesticides,  
19 pesticide related issues regarding the impact of  
20 proposed regulatory actions on human health and the  
21 environment.

22 The FIFRA SAP only provides advice and  
23 recommendations to the EPA. All decision making and  
24 implementation upon remains with the Agency.

25 A brief word now about financial



1 conflicts of interest. As the designated Federal  
2 official for this meeting, a critical responsibility is  
3 to work with the appropriate agency officials to insure  
4 that all appropriate ethics regulations are satisfied.  
5 In that capacity, the panel members are briefed on  
6 provisions of the Federal Conflict of Interest laws.  
7 In addition each participant has filed a standard  
8 Government Financial Disclosure report. I along with  
9 the Deputy Ethics Officer of the Office of Prevention,  
10 Pesticides and Toxic Substances in consulting...in  
11 consultation rather with the Office of General Counsel,  
12 have reviewed these reports to insure all ethics  
13 requirements are met.

14                   Public commenters - for members of the  
15 public requesting time to make public comment, please  
16 limit your comments to five minutes unless prior  
17 arrangements have been made. We do have a number of  
18 public commenters here today that have made  
19 arrangements and will take more than five minutes. For  
20 those that have not been preregistered for making  
21 comments today, please let me know or another member of  
22 the SAP staff know that you are interested in making  
23 public comments this afternoon.

24                   Now a word about the public docket.  
25 There is a public docket for this meeting, all



1 background materials, questions posed to the panel by  
2 the Agency and other documents related to the SAP  
3 meeting are available in the public docket. Slides of  
4 today's presentations that will be available within a  
5 day or two, perhaps even by the end of the day,  
6 background documents are also available on the EPA  
7 website for the FIFRA SAP. The agenda prepared for  
8 this meeting lists contact information for the docket  
9 so you can refer to the top of your agenda to see the  
10 docket information.

11 FIFRA meeting minutes. After this  
12 meeting is conducted, the SAP will prepare a report  
13 consisting of the responses to questions posed by the  
14 Agency, considering all background materials,  
15 presentations and public comments. The report serves  
16 as the meeting minutes, and they will be completed  
17 within ninety days after the close of this meeting.  
18 They will also be, the final report will also be made  
19 public, both on our website, the FIFRA SAP website, as  
20 well as in the public docket for this meeting.

21 Again, I wish to thank the panel for  
22 their participation. It's not always easy to take out a  
23 whole week out of one's schedule so I certainly  
24 appreciate everybody's efforts in participating in this  
25 meeting which I think will be very interesting and I

1 look forward to both a challenging and interesting  
2 discussion in the next two or three days.

3 **DR. HEERINGA:** Thank you very much, Jim.  
4 It's time I think we're set to begin and I'd like to  
5 open by introducing Dr. Linda Phillips who is Director  
6 of the Exposure Assessment Coordination Policy division  
7 of the Office of Science Coordination and Policy.

8 **DR. PHILLIPS:** Good morning. As the  
9 Chair said, I'm Linda Phillips with the Exposure  
10 Assessment Coordination and Policy division within  
11 EPA's Office of Science Coordination and Policy. Our  
12 acting director of the Office of Science Coordination  
13 and Policy had hoped to be here today to welcome the  
14 panel but unfortunately she is on travel, so she asked  
15 me to express her appreciation to the panel for  
16 participating in this important meeting.

17 As you already know from the materials  
18 you've read, this is an important milestone for the  
19 endocrine disrupter screening program. We have worked  
20 for many years on the development and validation of a  
21 candidate assay for the battery, Tier1 battery and now  
22 we have proposed a Tier 1 Battery and we look forward  
23 to the comments that we receive from the SAP on the  
24 adequacy of the battery in covering the mode of action  
25 for endocrine.

1 The development and validation of the  
2 candidate assay has been a collaborative effort between  
3 our SCP scientists and ORD scientists and we have a  
4 number of them here today so I'd like them to get up  
5 and introduce themselves so you know who the scientists  
6 are that have worked on this process and then I'll turn  
7 it to over to Gary Timm who will give an introduction  
8 of the ESP and then Les Touart will talk about the  
9 proposed battery.

10 **DR. HEERINGA:** Thank you, Dr. Phillips.  
11 You can introduce your staff.

12 **DR. RAY:** I'm Earl Ray, EPA Research  
13 Triangle Park, research laboratory.

14 **DR. WILSON:** Good morning, I'm Vicki  
15 Wilson, reproductive tox division and Office of  
16 Research and Development.

17 **DR. FOLKER:** Tammy Folker, EPA, Research  
18 Triangle Park, reproductive toxicology division.

19 **DR. COOPER:** I'm Ralph Cooper,  
20 reproductive toxicology division, Research Triangle  
21 Park.

22 **DR. LAWS:** Susan Laws, reproductive  
23 toxicology division, Research Triangle Park.

24 **DR. ANKLEY:** I'm Gary Ankley, ecology  
25 division, Duluth, Minnesota.

1 **DR. TEASY:** Joe Teasy, ecology

2 division, Duluth.

3 **DR. FRANCIS:** Anne Francis, I am the  
4 National Director for the Endocrine research program.

5 **DR. HEERINGA:** Thank you very much, any  
6 additional contributors please?

7 **DR. MILLER:** I'm Jessie Miller, I'm from  
8 OSCP.

9 **DR. GROVE** I'm Christiana Grove,  
10 Office of OSCP.

11 **DR. BURTOFF:** John Burtoff, OSCP.

12 **DR. HALL:** Dr. Hall, OSCP.

13 **DR. CULYA:** Jim Culya, OSCP.

14 **DR. HEERINGA:** Well, thank you very  
15 much, I think it's very useful to introduce the people,  
16 the staff, scientific staff who are working on this and  
17 I appreciate that. Gary Timm I think is going to do an  
18 overview for us.

19 **DR. TIMM:** Yes, thank you very much,  
20 good morning. As you'll hear two talks this morning,  
21 the one that I will give which is an overview of the  
22 endocrine disrupter screening program and I will start  
23 off by reminding people the statutory mandates and to  
24 fax recommendations and tell you about the development  
25 validation of the assays and the programs with clearly

1 an emphasis on Tier1 and then talk about some of the  
2 other mutation activities very, very briefly so that  
3 you get some idea of the other elements in the program  
4 and then last we will follow up with a presentation of  
5 the screening battery and illustrate how the screening  
6 battery works with a couple of model compounds or mode  
7 of action.

8 Try the computer into the microphone.  
9 EPA statutory authority dates back from 1996 with the  
10 passage of the Food Quality Protection act which  
11 amended the Federal Food Drug and Cosmetic Act and it  
12 actually mandated EPA to develop a screening program  
13 using validated assays to identify pesticides that may  
14 have an effect in humans similar to the effect produced  
15 by naturally occurring estrogen but that law also gave  
16 us some authority to extend that to other endocrine  
17 effects, made by the Administrator, and in language  
18 that I am sure was written by a lawyer, not a  
19 scientist, it could include non-pesticide chemicals  
20 that have an effect cumulative to that of a pesticide  
21 in which a substantial number of humans were exposed.

22 About the same time, I think it was  
23 actually about three weeks later, the Safe Drinking  
24 Water Act Amendment of 1996 was passed and they again  
25 gave EPA authority to require testing of chemical

1 substances found in the source of drinking water to  
2 whom a substantial population was exposed and this was  
3 really an add on, a build on to the basic authority in  
4 408C, it would operate in the very same fashion.

5 Well, in anticipation of the passage of  
6 the Act back in May of 1996, EPA gathered a number of  
7 interested parties, stakeholders, together and asked if  
8 they would be interested in forming an advisory  
9 committee to guide us through this process to help us  
10 select screens and tasks for the screening program.  
11 That committee was chartered October 16, 1996, it had  
12 broad representation, there were members of the  
13 pesticide industry, the chemical industry, state  
14 government, federal government, health and  
15 environmental people so I think that the expertise and  
16 the breadth was quite considerable.

17 At their very first meeting in December  
18 of 1996 there was some debate about the scope of the  
19 program and there was a quick consensus reached that it  
20 should expand beyond the statutory minimum of estrogen.  
21 They said yes, although estrogen probably has gotten  
22 the most press, the most play, sometimes what you're  
23 seeing really is not a feminization of males but really  
24 a demasculinization so you need to look at androgens  
25 too because what you're sometimes seeing is anti-

1 androgens and clearly thyroid had a huge impact on  
2 development as well so they studied them.

3                   Scientifically minimum program to be  
4 really credible needs to look at all three hormone  
5 systems and they said all the acts specified human  
6 health in the Environmental Protection Agency and the  
7 best evidence that we have for effects are really not  
8 on humans, but on wildlife. You clearly should look at  
9 ecological effects within the scope of this program and  
10 we know that chemicals other than pesticides are  
11 potential endocrine disrupters and so you need to look  
12 at the broader universe of chemicals to which people  
13 are exposed. If you're going to do all of this you  
14 really need to have a two tier approach to screening.

15                   In Tier 1 which should be composed of in  
16 vitro and in vivo screens, you will detect the  
17 potential of chemicals interactively and endocrinally.  
18 Chemicals that are positive in Tier 1 then on the  
19 weight of the evidence basis is you have multiple  
20 assays in Tier 1 would then go on to Tier 2 which would  
21 be multi-generation studies comprised of a range of  
22 taxa and they would be designed to provide the kind of  
23 dose response information that you would need for a  
24 hazard assessment.

25                   EDSTAC laid down for itself criteria for



1 the Tier 1 screens. It says it should, they should be  
2 able to detect all known modes of action for the  
3 endocrine end points of concern and they recognize that  
4 a battery was required because and a battery composed  
5 of both in vitro and in vivo systems because simple  
6 magnetic screens didn't exist for all modes of action,  
7 and so you needed to include the more complex multi  
8 model assays for Tier 1 and this is to some extent even  
9 a bit of a concern today that you will see a spectrum  
10 of opinion on and I think this afternoon you will hear  
11 some discussion about this formula. EDSTAC clearly  
12 wanted to minimize false negatives, EDSTAC clearly  
13 wanted to look at the full life cycle of the hormone  
14 from synthesis, to release in the blood stream, to  
15 finding its way to its target tissue, binding with a  
16 receptor, the downstream consequences from that binding  
17 and finally metabolism and elimination of the hormone,  
18 because they said at any of these various points  
19 there's a potential for interference with the system.

20 They felt that you should include a  
21 sufficient diversity among endpoints, to permit a  
22 weight of evidence conclusion, so, to that end there  
23 are multiple endpoints, the in vitro assays and the  
24 assays and the end points are complimentary.

25 EDSTAC, as I mentioned before, clearly

1 wanted to maximize sensitivity to minimize false  
2 negatives and that of course doesn't mean you can  
3 forget about false positives but that was the bias that  
4 was built into the system and they noted that the in  
5 vitro mechanistic screens are highly sensitive, but  
6 that as I mentioned before the in vivo apical screens  
7 were necessary to encompass all the known modes of  
8 action and to take metabolic activation into account  
9 and knowing that there are some differences between  
10 species, it should include a sufficient range of  
11 taxonomic groups to represent the differences in the  
12 endocrine system and metabolism and to that end fish  
13 are included because they are fish, they differ to some  
14 extent in hormones, they clearly differ in the way that  
15 they are exposed and they also differ to some extent in  
16 metabolism.

17                   So the battery of assays that were  
18 recommended by EDSTAC were the estrogen receptor  
19 binding in rat uterine cytosol or the transcriptional  
20 activation system, the androgen receptor binding in  
21 using rat prostate cytosol or androgen transcriptional  
22 activation system. A steroidogenesis assay utilizing  
23 minced rat testes as the source of the enzymes and then  
24 the in vivo components, the uterotrophic, the  
25 Hershberger, a pubertal female, an amphibian

1 metamorphosis assay or a thyroid, and the fish gonadal  
2 recrudescence assay, fish are aquiescent and then they  
3 become up to reproductive capacity when the APG axis  
4 turns on In the springtime.

5           The, the EDSTAC also noted that these  
6 aren't the only assays that were available. They  
7 looked at a large number of candidates and they said  
8 the pubertal male might be a good substitute for the  
9 pubertal female and the adult male might be also a  
10 substitute for the female. But if you do use one of  
11 the male assays you would need as a complement,  
12 aromatase because the male is not a very good model to  
13 detect, not very sensitive to detect interferences with  
14 aromatase.

15           And they didn't recommend a specific  
16 protocol for in utero lactation but that was a goal.  
17 They said, you know, that would really be the best  
18 thing if we could get a screen that looked at the in  
19 utero phase and of course this panel looked at that  
20 issue and gave us a recommendation that there was  
21 nothing that was available, and EPA searched for a  
22 number of different protocols, nothing that really  
23 looked like a screen, it was a more complex, more  
24 expensive assay than the screening profiles.

25           For Tier 2 EDSTAC recommended the

1 mammalian 2-gen with some endocrine endpoints added to  
2 it, an avian reproduction test, amphibian growth  
3 reproduction fish life cycle and the invertebrate mice  
4 life cycle. EPA accepted the EDSTAC recommendations.  
5 We published that on December 28, 1998 in the Federal  
6 Register and proposed that as policy and the basis for  
7 the EDSP, stating that we thought that the  
8 recommendations that EDSTAC gave were scientifically  
9 rigorous, they represent the best science at the time  
10 and we felt that obtaining a consensus from such a wide  
11 group of stakeholders was quite a remarkable feat and  
12 was quite compelling.

13 EPA then, and I don't have a slide on  
14 this, but we went to the SAP in 1999 with that program  
15 and got some additional advice from the SAP, the SAP  
16 said that we should focus on about fifty to a hundred  
17 chemicals in the initial group to really try out the  
18 Tier 1 battery. The EPA went from that point on, we  
19 also looked at some items between what the EDSTAC  
20 recommended and we found that the existing off the  
21 shelf assays really were not suitable for use to  
22 detect chemicals. They were great for pharmaceuticals  
23 but the pharmaceutical industry had not optimized them  
24 to detect compounds of lower focus.

25 So we went forward and carried out three

1 activities to implement the program, priority setting  
2 or picking chemicals for that first tier of 50 to 100,  
3 jumping procedures that would be needed to implement  
4 the law, typically the Agency does that, the Agency has  
5 to develop detailed procedures to implement authorities  
6 that were granted by statute and then the biggest  
7 activity of all of course was the development and  
8 validation of the assays.

9 I'll mention the first two briefly just  
10 sort of to provide perspective. In terms of priority  
11 setting we, because the heightened chain did not work  
12 and we didn't feel like we had the time and resources  
13 to, to optimize it, we went ahead and proposed an  
14 approach and after comments adopted it, it was based  
15 strictly on exposure and we were looking at pesticide  
16 active ingredients, looking at food, water, residential  
17 and occupational exposure pathways and high production  
18 volume, inerts, pesticide active and HPB inerts looking  
19 at human and ecological effects biomonitoring data and  
20 also data that showed the presence of chemicals in  
21 water and air.

22 We then, using that approach, drafted a  
23 list of chemicals for initial screening and published  
24 that on June 18, 2007 for public comment. That list  
25 contained sixty-four pesticide actives and nine high

1 production volume pesticide inerts and again because  
2 these chemicals were chosen strictly on the basis of  
3 exposure, not at all habit information they are not  
4 a list of known or likely endocrine disrupters.

5 In terms of procedures in parallel with  
6 this other activity, we drafted a policy as to how to  
7 implement this authority, published for people to  
8 comment on the pest ordered templates and issued  
9 information collection requests which is required  
10 anytime an Agency requests information from a regulated  
11 entity and that was published on December 13 ,2007. In  
12 that notice EPA said it would direct test orders under  
13 408P and also using its Authority under FIFRA 3(c)2(b )  
14 to the technical registrants for the active  
15 ingredients.

16 For the inerts it would send orders  
17 under the FFDCA408P authority for manufacturers and  
18 importers and now the big activity. The validation.  
19 The validation is required not only by FFDCA, the part  
20 of the law that I read to you in the very beginning,  
21 408P, but also by the ICCVAM authorization act of 2000.  
22 It was recommended by EDSTAC and it was later endorsed  
23 by OECD, Organization for Economic Corporation and  
24 Development which now as a matter of policy says that  
25 new test guidelines need to have validated methods as

1 their basis. The validation has been defined as an  
2 assessment of the reliability, high relevance of a test  
3 method for a particular purpose, relevance being the  
4 extent to which test methods will correctly predict and  
5 measure biological effective interest and reliability  
6 to the extent to which a test can be performed  
7 reproducibly within laboratories and among laboratories  
8 and over the course of time.

9 A number of principles were set down by  
10 ORD at its conference back in 1996 by ICCVAM, by ECVAM,  
11 generally agreed upon that one must clearly articulate  
12 the scientific and the regulatory rationale for the  
13 method. One must describe the endpoints of the test  
14 method to a biological effect for the toxicity of  
15 interest, that there should be a formal detailed  
16 protocol available such that a competent laboratory who  
17 has not run the assay before can in fact follow that  
18 protocol and conduct the assay. There must be an  
19 assessment of variability again within labs, between  
20 labs, and over time. An assessment of the performance  
21 of the assay with known reference chemicals. It's like  
22 having the answer key to a quiz, giving the quiz. You  
23 must describe the limitations of the assay, pay  
24 attention to data quality issues, and typically conduct  
25 the validation in GLP laboratories, and then make the



1 data available for public inspection and send it to an  
2 independent scientific review.

3           Now even with the publication of these  
4 methods and they were really geared initially to assist  
5 the development of alternative assays; that is,  
6 methods, in vitro methods that would be replacing in  
7 vivo methods. The community developing these  
8 alternative methods was having difficulty and so as a  
9 matter of practice as they gained experience in the  
10 literature for validating alternative methods some of  
11 these concepts came out. The alternative test method  
12 should consist of two parts, the test system and  
13 prediction model. That the prediction model is an  
14 algorithm for converting the in vitro data into a  
15 prediction of in vivo toxicity and the validation is  
16 essentially in this approach, a test or measure of the  
17 performance of the prediction model and that the  
18 prediction model needs to be developed prior to  
19 validation because it has to be a prospective  
20 evaluation of the prediction model, not a retrospective  
21 one, and that the test set of chemicals used in  
22 validation should be different from the set used for  
23 model building so you have the idea again of a train  
24 set and a test set.

25           Well, there was a very, very different

1 set of approaches, a different discipline for the eco  
2 toxicity test methods and I would guess that that's  
3 been around for what probably twenty five, thirty  
4 years. They were conducting what they called ring  
5 tests where a new method would be tested across  
6 laboratory with a limited number of chemicals to test  
7 the reproducibility of a method. The relevance was  
8 assumed; they did not worry about relevance because  
9 they said we're testing him in an environmentally  
10 relevant species. They didn't have a prediction model  
11 because they were relying on direct observation of the  
12 toxicity of interest looking at critical life  
13 processes, and they based their standardization after  
14 the fact on the protocol assessment rather than on  
15 prevalidation. So recognizing that more guidance  
16 needed to be given in the area of test method  
17 validation OECD decided to develop what they called  
18 Guidance Document Number 34, to provide practical  
19 guidance on the validation test methods. And it was  
20 really to provide some not only guidance but  
21 flexibility in applying the criteria and guidance  
22 document 34 recognized that the amount and kind of  
23 information needed and the criteria that would be  
24 applied to a new test method would depend upon the type  
25 of test. Its purpose and use and what's known about

1 the test, how long it's been around, whether it's a  
2 mechanistic test, et cetera.

3                   Guidance Document 34 I think sharpened  
4 the debate but I don't think it settled the issues.  
5 Guidance Document 34 came along in 2005, we had already  
6 been in business trying to validate things for some  
7 time and we looked at what we were doing in light of  
8 the guidance that we were receiving from our advisory  
9 committee as well as from OECD and said Tier 1 is for  
10 screening, it's really for the detection of potentially  
11 interactive endocrine system. And it's a battery of  
12 assays, it's not a single assay and the assays are  
13 already there to complement each other and the strength  
14 of one assay should offset the weaknesses in another.  
15 There...even though they've been around for thirty or  
16 forty years, in one sense they're new assays, they have  
17 not been validated before and they're not replacements  
18 to the existing streams so that means we have a limited  
19 number of reference chemicals, and frequently the best  
20 reference chemicals are not pesticides or chemicals we  
21 find in the environment but in fact pharmaceutical  
22 compounds and there are practical limitations regarding  
23 the numbers of tests that we run during validation and  
24 the numbers of chemicals that we test especially when  
25 you get into in vivo methods.

1 So we said it's important for us to  
2 challenge the assay with carefully selected benchmark  
3 chemicals. That number of chemicals will vary with the  
4 assay, maybe twenty, fifty for in vitro screens but  
5 it's going to be much more limited to the in vivo  
6 screens, five perhaps to fifteen, and much more limited  
7 than that for Tier 2.

8 The goal we set based upon advice we  
9 were given that somewhere around ten to twenty five  
10 percent of the chemicals would be negative and we  
11 didn't always meet that goal. I think that the  
12 probably the clearest example of not meeting that goal  
13 were the pubertal assays where we considered probably  
14 close to a hundred chemicals, picked one to run as the  
15 negative, and found that in fact it did not...it was  
16 not a negative. And that was frustrating, but in fact  
17 when you look at the assay and you look at the thyroid  
18 active compound assay and they don't interact with the  
19 estrogen and androgen system and vice versa and so  
20 there is still evidence of specificity in that assay  
21 even though we failed to find that clear negative that  
22 we wanted to find.

23 So in validating the assay, EPA asked  
24 the question is the variability satisfactory for the  
25 purpose and with the results that we wanted to obtain

1 with the benchmark chemicals. How do we proceed, what  
2 is the process, this is the process that was found in  
3 the ICCVAM 1997 document. First of all I'm start  
4 talking test method development. You go into the  
5 library because you can save a lot of time in the  
6 library versus going to the lab so we had scientific  
7 literature review prepared to look at the relevant  
8 kinds of assays and recommend to us what protocols  
9 we've got were the best to proceed with. Took that  
10 protocol, tried to demonstrate how feasible that  
11 protocol worked, demonstrate its relevance to the end  
12 points, and then work on optimizing the conditions of  
13 the protocol and when we were satisfied that we could  
14 do that, then we went into an inter-laboratory study  
15 with three to five laboratories, and then sent, we  
16 collated all that information, put it into an  
17 integrated summary report and all that information in  
18 the back up studies went to the peer review panel and  
19 they gave us their report, we developed a response to  
20 comments to the peer review panel and then we moved to  
21 the fifth stage which is regulatory assessments which  
22 is really where we are now, the proposal to the Tier 1  
23 battery, your review of that battery, advice to us and  
24 then adoption of a Tier 1 battery.

25 There was a big challenge of how to get

1 everything done and we worked with OECD on the  
2 guidelines of international interests. The methods  
3 there would be developed and validated through OECD and  
4 interestingly enough the DUX was a leading country on  
5 most of those test guidelines. The test methods that  
6 were not of interest to other member countries in OECD  
7 were developed and validated by EPA with advice from  
8 our advisory committee, the Endocrine Disruption  
9 Methods Validation Advisory Committee and this is kind  
10 of a scoreboard of where we now stand. As you can see  
11 the uterotrophic assay was completed and peer reviewed  
12 through OECD, the Hershberger went to a similar process  
13 except EPA serves as the lead country on that assay,  
14 leading laboratory, the estrogen receptor  
15 transcriptional activation assay was validated by  
16 Japan, through OECD and you can see they have the adult  
17 male, pubertal female, pubertal male, AR binding,  
18 aromatase assays were done by EPA. Amphibian  
19 metamorphosis assay in fish, again, EPA leads validated  
20 and peer review in conjunction with OECD.  
21 Steroidogenesis assay I'll tell you a bit more about,  
22 but it is to be validated next month and the ER binding  
23 assay will probably be validated I should say peer  
24 reviewed, both of those peer reviewed, next month for  
25 steroidogenesis and peer review for ER binding in June

1 of this year.

2                   This slide compares the recommendations  
3 of EDSTAC with those proposed by EPA. As you can see  
4 I've highlighted in the right column those differences,  
5 the first being the androgen receptor transcriptional  
6 activation assay, we have not yet validated that assay.  
7 Steroidogenesis, they recommended the minced rat testes  
8 assay, we went through a prevalidation with that assay,  
9 we found that variability was very high, but the real  
10 coup de grace for that assay was the fact the lighted  
11 cell is only about one to two percent of the match of  
12 the testes and your typical site of toxicity assays  
13 could not differentiate between the rest of the cells  
14 and the lighting cells so it was felt that we really  
15 could not tell when we had a lighting specific toxigen  
16 versus a general toxigen and we didn't see any good way  
17 to solve that problem. So faced with two difficulties,  
18 and knowing that our lab down at RTP and some of the  
19 literature had suggested that the H295R assay looked  
20 promising in that it was probably the only cancer cell  
21 line that we were aware of that had all of these  
22 enzyme, the steroidogenesis pathway. We shifted our  
23 resources to that assay and the validation of the core  
24 chemicals, testing the core chemicals, as I noted  
25 validation report is in preparation and that will all



1 go to peer review this next month.

2           The other assay, the next one down that  
3 is different, it's the fish gonadal recrudescence  
4 assay, I have described that briefly to you and we  
5 switched to the fish short term reproduction assay  
6 because we found that the variability in the  
7 recrudescence assay was just much too huge and so it  
8 was not a sensitive assay.

9           Placental aromatase assay, we actually  
10 validated the placental aromatase and human recombinant  
11 aromatase assay, we felt that given the ease of the  
12 recombinant assay compared with the placental aromatase  
13 assay that that's the one we would require. Obviously  
14 if somebody is bound and determined to go with the  
15 other assay, they could petition us to use that, but we  
16 suspect that, we opted for the recombinant aromatase  
17 assay.

18           The adult male assay went through a  
19 validation program. It was originally anticipated that  
20 this would be a very strong specific mode of action  
21 assay using hormone measurements as kind of a  
22 fingerprint for mode of action. Unfortunately when it  
23 got to the validation it seemed as though that really  
24 no longer was the case. There was too much variability  
25 in the hormone measurements, they were measuring out

1 only the thyroid hormones and the steroid hormones but  
2 LH and FSH and the idea was that you could get, you  
3 could really get an understanding of where in the HPG  
4 axis you had a problem by looking at the different  
5 hormone measurements, but that was not practical and so  
6 you were left really with the histopathology of the  
7 main endpoint. EPA felt that that really put the adult  
8 male at a big disadvantage relative to the pubertal  
9 assays.

10 The last one as I mentioned before was  
11 the Utero-lactation assay which you gave us advice on  
12 about a year ago and we abandoned work on that as a  
13 Tier 1 assay.

14 Just the next few slides do summarize  
15 things. Everything is supposed to converge and I know  
16 that physicists will say a pre-body collision is a very  
17 rare event. We're going to try to have that happen,  
18 having assay validation, priority setting, and  
19 implementation procedures all come together in August  
20 of 2008. We have been told by our appropriations  
21 committee that this is your deadline and I don't know  
22 what happens if you break it, whether the  
23 appropriations committee says, sorry, you're out of  
24 money or what but this we're taking this very, very  
25 seriously so we will issue in August 2008 a Federal

1 Register Notice of our final battery, issue the final  
2 list of chemicals and publish the final policies and  
3 issue test orders.

4 So what happens after August 2008?

5 Well, there's still work to be done, clearly. We need  
6 to complete the validation of the Tier 2 assays so that  
7 people have a place to go with their options on Tier 1  
8 and so the mammalian 2-gen after the end points were  
9 added in the 1998 guidelines would work, they would be  
10 acceptable. However, we think we can improve upon  
11 them, we're...our efforts are now directed toward a  
12 guilty, hefty modified protocol on an extended one  
13 generation test in which more animals are carried  
14 forward. We have greater sensitivity for some of the  
15 androgen endpoints and, plus we're picking up neuro  
16 tox, developmental neuro tox and developmental immuno  
17 tox, so we think that that's an improvement, it will be  
18 probably an improvement over the expanded two, and  
19 we're working with OECD to insure that that becomes an  
20 OECD guideline if that is an acceptable satisfactory  
21 procedure.

22 We're working on protocols for the avian  
23 2-gen, for the amphibian growth reproduction study, for  
24 a fish 2-gen, for a Mysid 2-gen and of course we're  
25 looking at having all of that completed by the end of

1 2010 which is about the time we expect to have data in  
2 from Tier 1 and have the Agency review those data and  
3 be in a position to make some decisions on what  
4 chemicals need to go in Tier 1 and what do not. So in  
5 summary it's a two tier program, chemical assays for  
6 Tier 1 screening battery includes both in vitro and in  
7 vivo, mammalian and nonmammalian assays that have gone  
8 through validation process and peer review, EPA  
9 considers them to be validated and ready for use. We  
10 will implement the screening programs on the first  
11 group of chemicals, seventy three chemicals in August  
12 2008, with orders and protocols for the assays in the  
13 Tier 1 battery. We'll continue to plug away on Tier 2  
14 with a target of 2010 and that brings us back to again  
15 the purpose of this meeting to review our battery, Tier  
16 1 battery and to give us advice with respect to the  
17 battery's ability to meet its intended purpose which as  
18 EDSTAC articulated, it's to distinguish chemical  
19 substances that interact with the endocrine system,  
20 that is the EAP system, from those that do not and it  
21 should then provide a reasonable assurance both to EPA  
22 and to all stake holders that upon completion of Tier 1  
23 screening the chemical will either have low or no  
24 potential for endocrine, that is EAT activity, or if it  
25 in fact such has such a potential. Thank you very

1 much.

2 **DR. HEERINGA:** Thank you very much. At  
3 this point I'd like to turn to the panel to see if you  
4 have any questions and clarifications for Dr. Gary  
5 Timm. Dr. Denver?

6 **DR. DENVER:** Bob Denver, University of  
7 Michigan, I'm curious about the ability to refine or  
8 add to the Tier 1 screenings and if there is an ability  
9 to do that but that has not been mentioned.

10 **DR. TIMM:** There clearly is the  
11 intention in the future of doing that, I mean one of  
12 the purposes for the SAP's earlier recommendation to  
13 test a limited number of chemicals to stop and evaluate  
14 what you have, look at your current Tier 1 battery, the  
15 other component of that is to look at how the science  
16 has changed and if there's something better there to  
17 put it in. In terms of whether we would permit  
18 substitutions now or not, I don't think EPA has really  
19 reached a decision on that, I tend to think not just  
20 because that's a difficult thing to do and one has to  
21 go through validation but we will see what things look  
22 like, we're open but clearly we've got a job to do and  
23 not much time in which to do it.

24 **DR. BROWN:** Terry Brown, what is the  
25 status of the energy receptor transcriptional

1 activation assay at this point? I know there have been  
2 problems in the past with the patent restrictions and  
3 you indicate that it's still in development or is that  
4 not the case?

5 **DR. TIMM:** The androgen receptor binding  
6 assay we actually have one that's been developed in our  
7 laboratory down in Research Triangle Park, we just have  
8 not had the resources to carry it through and validate  
9 it. It's been used in probably a dozen or more  
10 laboratories by now and the developer may want to add  
11 to what I'm saying but it's something that possibly  
12 could be validated using a paper exercise if enough  
13 laboratories have tested enough chemicals. That's  
14 something we want to look into. In terms of the other  
15 activities, estrogen receptor transcriptional  
16 activation assay has been validated by Derry of Japan.  
17 You will also hear this afternoon about a commercial  
18 system, the little cell system which does that. Our  
19 intention is to develop, I think there's a lot of  
20 interest in OECD and some of it really worked at OECD  
21 to develop test guidelines for activation,  
22 transcriptional activation assays.

23 **DR. HEERINGA:** I'd like to thank you  
24 very much, Dr. Timm. At this point I think we're set  
25 for a presentation from Dr. Les Touart, and I think

1 since we started at nine I'm willing to go a little  
2 while longer before our break and I think, Dr. Touart,  
3 I think your presentation is possible before we break.  
4 Panel members, it looks like copies of the slides are  
5 being circulated.

6 **DR. TOUART:** Thank you, Chair, and my  
7 name again is Les Touart and I'll be providing a  
8 presentation on the Tier 1 screening battery basically  
9 the rationale for the battery and provide some examples  
10 of some compounds and how they play out in some of the  
11 assays. The first point I'd like to make is what it  
12 is, the Tier 1 screening, and the goal of the Tier 1  
13 screening as described by the staff is to detect  
14 chemical substances or mixtures capable of interacting  
15 with estrogen, androgen or thyroid hormone systems.  
16 What it is not...the objective of the Tier 1 screening  
17 is not to determine dose response relationships,  
18 confirm the mechanism of action or determine the  
19 adversity of the chemical's effect on reproduction  
20 and/or development. I think these are elements that  
21 the EDSTAC believed were more appropriate in the Tier 2  
22 dealing with more definitive tasks. You know, the Tier  
23 1 was designed to be more qualitative for screening, to  
24 provide suggestive evidence that a potential for  
25 interaction was possible.



1 Just to kind of go back and preview a  
2 little bit in the context of the endocrine system and  
3 these are the realities that it's an integrated, fairly  
4 complex, you know, system, it's designed to maintain  
5 homeostasis so with that there's a built in key feature  
6 which is the negative feedback. You know, hormones as  
7 they reach certain titers will feed back into the  
8 system so that they can be controlled and this is  
9 important in again maintaining the homeostasis. The  
10 estrogens, androgen, and the thyroid systems, you know,  
11 we understood are subparts of part of the endocrine  
12 hexis, and in investigating the potential for  
13 interaction or disruption of these systems one has to  
14 include the broad axis themselves. The system can be  
15 perturbed at multiple sites and by multiple mechanisms.

16 The next few slides are just to give a  
17 little bit more diagrammatic, you know, context, you  
18 know, for this, which I'm sure you all are familiar  
19 with context of the HPG axis as an example, you know,  
20 where you have hormones coming from hypothalamus to  
21 pituitary which then, you know, move down, stimulate  
22 production of the steroids in terms of the androgens,  
23 estrogens and feedback, you know, mechanisms and the  
24 axis is designed to generate a variety of and control a  
25 lot of processes in terms of food production and the

1 like.

2 Another example, just to quickly go  
3 through these is HPT and thyroid, you know, axis.  
4 Again the context, you know, here it's a complex  
5 system, there are multiple chemical signals that go  
6 through a lot of coordination that's needed for these  
7 examples hereto of sites where things could actually  
8 disrupt and interfere with the normal function of the  
9 axis.

10 The next slide is very designed to show  
11 a broader integration. Can't we look at the HPG axis,  
12 you know, saying, well, you can't look at the HPG  
13 axis, you're left saying, you know, these do interact,  
14 interact with other endocrine, you know, systems and  
15 mechanisms so they go very broadly in the context in  
16 controlling many processes in living organisms.  
17 Another context is to evaluate effects on a particular  
18 hormone, you really need an intact, you know, system,  
19 intact axis to be able to evaluate the full potential  
20 of effects that these will occur. To generally sum up  
21 the considerations here, it's, you know, given the  
22 complex interactive nature of the endocrine system it's  
23 clear that chemicals should be screened for their  
24 apical activity, the ability to alter things like  
25 growth, development, reproductive processes, rather

1 than just for their sex steroid activity in in vitro  
2 assays. If the objective is indeed such as effectively  
3 detect their potential to disrupt these endocrine  
4 regulated processes.

5 In developing the screening battery and  
6 the proposal to go forward, I've been following the  
7 EDSTAC recommendations, it's designed to insure  
8 detection of the estrogens, androgens, and thyroid  
9 hormonal systems. I think the, you know, key context,  
10 it would be naive to think that one could look at say  
11 estrogen, you know, alone without really considering  
12 the other, you know, hormones and the interactions that  
13 could take place because interferences, you know, even  
14 along those lines would have complications that would  
15 be manifest. The battery fulfills the EDSTAC  
16 recommendation for including a range of taxonomic  
17 roots. It includes sufficient diversity of endpoints  
18 to maximize sensitivity and minimize false negatives  
19 and I think the other context here as I've said is  
20 really designed to help minimize false positives too  
21 by having multiple assays and multiple endpoints, it  
22 kind of works both ways to use the weight of the  
23 evidence in determining what you have.

24 It emphasizes apical assays to provide a  
25 more comprehensive assessment, again, the concept of

1 needing those intact, you know, axis and looking at the  
2 summary outcomes of various processes involved in the  
3 development of reproduction.

4           It meets the overall objective of  
5 detecting the potential and the mediated effects  
6 regardless of mode of action. The assays, and Gary  
7 kind of mentioned these, but the ones that we are  
8 proposing in this battery include the steroidogenesis,  
9 it's an in vitro, you know, assay, the estrogen  
10 receptor binding assay, the estrogen transcriptional  
11 activation assay, the androgen receptor binding assay,  
12 an aromatase assay, not an in vitro, and then from in  
13 vivos we have a uterotrophic assay, a Hershberger  
14 assay, pubertal female assay and pubertal male assay.  
15 These are all our own assays.

16           Then there's amphibian metamorphosis and  
17 the short term reproduction. This slide is to display  
18 the various assays within the battery and to compare  
19 them across various modalities that we are trying to  
20 obtain information on in terms of the battery's ability  
21 to indicate the potential for some interaction. In the  
22 first column dealing with the estrogen agonists and the  
23 assays that are designed to work with that include the  
24 ER binding, the ER transcriptional activation,  
25 uterotrophic pubertal female and a history production

1 screen. Context here with the binding assay, that  
2 identifies whether you actually bind with the receptor.  
3 Transcriptional activation would actually give you  
4 information on function and be able to indicate that  
5 there's agonism that would be occurring. The  
6 uterotrophic is sensitive for, you know, the estrogen  
7 receptor mediated, you know, processes and so it  
8 provides a sensitive indicator of that fact. But the  
9 pubertal female and the fish referral, you know, these  
10 are intact organism, you know, tests that would include  
11 the entire HPG, you know, axis and cover the taxonomic  
12 range and again, the EDSTAC concept was to try to cover  
13 the bookends of the perfect plan. In terms of the,  
14 they've got them at locked processes, the other element  
15 that this brought in is roots of exposure in terms of  
16 the pubertal female or the rodent study would be more  
17 of a dietary exposure. For the fish in this case it  
18 would be more of a, I guess it depends on dermal  
19 inhalation since it's exposure from the water coming  
20 across the gills so there's some differences in that  
21 context. For the estrogen antagonist we have ER  
22 binding because the binding assay doesn't differentiate  
23 between the agonist or the antagonist.

24                   The ER transcriptional activation has  
25 potential for actually identifying antagonism but it

1 hasn't been validated for that component yet so that's  
2 another reason that we've included the ER binding, the  
3 transcriptional activation, if it's not positive as an  
4 agonist, we could kind of secondarily interpret that it  
5 has a very, a potential for being an antagonist, but  
6 again that hasn't been fully validated in its context  
7 at least in all cases but the other thing is that the,  
8 we're limited then in terms of in vivo assays and the  
9 intact, you know, HPG axis context with the pubertal  
10 female and the fish repro, and that's a context in  
11 terms of the, you know, being able to have, you know,  
12 intact organisms and the taxonomic diversity.

13                   When we get to the androgens for both  
14 the androgen agonists and the androgen antagonism. We  
15 have AR binding similar to ER binding. It, it will  
16 detect the ability of the receptor to be bound.  
17 Hershberger assay, which is a castrated rodent version  
18 that we use and within this context it provides a  
19 sensitive indicator for the agonism and                   antagonism  
20 of androgens. The pubertal male has an intact HPG as  
21 does the fish repro. And again the intact HPG with a  
22 taxonomic spread is covered with that one.

23                   For steroid synthesis modulation we  
24 thought, you know, for both the synthesis in terms of  
25 the androgen as well as the estrogen. The

1 steroidogenesis assay which is a recombinant assay  
2 covers both and aromatase is also utilized but it's for  
3 very, for the next final step in the process which  
4 would be the conversion of the testosterone to the  
5 estrogen finally.

6 And then again for the, with both  
7 pubertals and the fish, we got the full HPG axis  
8 covered so any interference in steroid metabolism that  
9 would occur there or through any other process within  
10 the system that adrenal system in terms of adrenal  
11 corticoids. You know, those would be picked up in that  
12 context. For the HPG and we have the pubertals and  
13 then the fish repro. For the thyroid we really have no  
14 in vitro, you know, screens that have been able to  
15 conform to a point that would be useful that we have  
16 available to assist in identifying a particular  
17 mechanism, but with the intact HPG, with pubertal male,  
18 pubertal female we do have endpoints related to the,  
19 you know, hormones and the gland histology and then  
20 with amphibian metamorphosis we provide, you know, a  
21 developed male life stage and multiple end points for  
22 looking at final and I think the context here with the  
23 variety of life stages that we have in terms of  
24 pubertal or maturing individuals in the pubertal assay.  
25 In the fish assay we're dealing with reproductively



1 active adults and then with the amphibian assay we're  
2 dealing with larval stages which have relationships to,  
3 you know, to other like fetal developments and things  
4 and analogous frames so the context with multiple life  
5 stages which including intact HPG or HPT we've covered  
6 a life raft of potential interactions with the  
7 estrogen.

8                   Okay, and just to briefly kind of go  
9 back over, you know, the modalities as far as which  
10 assays, you know, fit within the particular modalities,  
11 HPG is covered with the male pubertal and female  
12 pubertal and fish reproduction. Subsets of the HPG  
13 which include the estrogen androgens and then the  
14 steroidogenesis include some of the in vitro assays.  
15 On the estrogen side, you know, we have the binding  
16 transcriptional activations and then the female  
17 pubertal and fish reproduction. The androgen sides,  
18 the AR binding, Hershberger, the male pubertal and fish  
19 reproduction. The context for having both the female  
20 and the male pubertals was that the male pubertal  
21 couldn't, you know, cover the, in an intact HPG some of  
22 these estrogen endpoints that would be of use and again  
23 we wanted to make sure that we had the taxonomy spread  
24 out with both pubertals included that provides full  
25 coverage there but also allows interpretation in terms

1 of the other axes in terms of the thyroid axes. For  
2 thyroid it's just the male female pubertals and then  
3 the amphibian metamorphosis.

4           What I want to do now is go into at  
5 least in going back to the modalities and then look at  
6 some of the examples that we have for the assays  
7 related to those modalities. For the estrogen pathway,  
8 ER binding again is there to detect chemicals that bind  
9 with the receptor. The transcriptional activation is  
10 there to detect the estrogen receptor interaction and  
11 function and can differentiate the ER agonists. The  
12 Uterotrophic which, the preferred method that we are  
13 putting forward is the subcutaneous. At peak exposure  
14 it is an in vivo, it detects chemicals that act in vivo  
15 but also incorporates metabolism. The pubertal female  
16 and the fish brain are designed to detect compounds  
17 that act on the full estrogen system as intact HPGs.  
18 The first example of estrogen compound, methoxychlor,  
19 it's an organic chlorine insecticide, methoxychlor has  
20 been shown to be weakly active in in vitro ER binding  
21 assays, methoxychlor and its metabolites are much more  
22 active in a compound, and one of these is an ER alpha  
23 agonist but an ER beta antagonist and an androgen  
24 receptor antagonist as well.

25           In looking at the assay responses I'm

1 not surprised the ER binding and the transcriptional  
2 activation invoked weak responses in terms of the  
3 parent methoxychlor. In the uterotrophic assay when  
4 metabolism's incorporated, we get a definite positive.  
5 In the pubertal female there's a positive which  
6 substantiates the effect in terms of accelerated  
7 vaginal opening and age at first menstruous so multiple  
8 endpoints which are influenced by an estrogen hormone  
9 itself. The fish screen also positive, inducing a male  
10 tautologen which is a key endpoint within that assay  
11 but also reducing egg production and just to go through  
12 at least briefly some of the ASI's in this context.

13           The uterotrophic assay, you see the  
14 definite increase of the effect in terms and this is  
15 average data across three labs that were used in the  
16 OECD validation program and again we've heard the obex  
17 animals the subcutaneous exposure but the pubertal  
18 female and I think, I think the, what's indicated here,  
19 again, at both concentrations we have significant  
20 effects. The significance is identified by the colors  
21 of the cells to indicate that at both test, you know,  
22 concentrations there were significant effects, seeing  
23 the age at the vaginal opening, age at first address  
24 and also on the cytotoxicity of the organisms.

25           This slide is just to indicate that the

1 pubertal female includes some thyroid end points but  
2 for this estrogen active compound, you know, the end  
3 points utilized for detecting thyroid activity, these  
4 were all negative in context, so that the context here  
5 is end points that are related to a particular  
6 modality, you know, will respond to a modality but for  
7 other modalities, you know, they will not so I'll just  
8 say that you can't get multiple mechanisms in action,  
9 but I think we'll have some examples of that later.

10 In terms of the, an estrogenic effect in the  
11 male, we see again on the male side a significant  
12 increase in vitellogen occurring which is a sensitive  
13 endpoint of the assay. There was also some significant  
14 findings in terms of the testosterone in reduction  
15 there from the, from the compound.

16 And this may be related to some of the  
17 androgen receptor antagonisms that is also associated  
18 with methoxychlor in terms of multiple pathways that  
19 might be involved. One of the apical endpoints, I'll  
20 vet it and then I'll look for this particular compound,  
21 but we can see and again, this slide is looking at  
22 cumulative number of eggs spawned and there's, in this  
23 case pre-exposure time the number of eggs identified  
24 and then the post exposure from time zero you can see  
25 that once exposure is initiated there is a effect on

1 the number of eggs spawned and the significant  
2 difference, you know, identified in the high exposure  
3 group.

4 The next example compound that was  
5 investigated through the estrogen assays is just an IA,  
6 a controversial compound. Its main use is in the  
7 synthesis of polycarbonate plastics. It's been  
8 demonstrated previous to be estrogenic in vitro and  
9 mixed results in vivo.

10 And these were played out again with the  
11 assays in our battery in terms of the ER binding and  
12 the transcriptional activation both showing, you know,  
13 positives, you know, indicating that, that it's an  
14 agonist. The uterotrophic assays subcutaneous also  
15 positive to indicate that at least in the in vivo  
16 system, you know, there is a positive response. The  
17 pubertal female, you know, was negative in this case.  
18 The fish screen was positive indicating also like we  
19 have seen for other estrogens induction of the male  
20 vitellogen and then decreasing in female egg  
21 production. The suggestion here is that perhaps there  
22 is some type of metabolism, you know, that would be  
23 going on that may be say detoxifying the compound in  
24 pubertal females since this is a dietary route. The  
25 subcutaneous with the uterotrophic and then in the fish

1 brain where you have transfer across the gills, you  
2 know, they tend to corroborate each other in a context  
3 so that would raise the question as to whether dietary  
4 route would be effective in terms of the, of the  
5 disphenol, you know, A type of mechanism involved, so  
6 there's other data again like you saw with  
7 methoxychlor, there is a dose related response in terms  
8 of the action and the increase in terms of either size.  
9 For the pubertal female the only significant findings  
10 in the study were on weight gain but the significance  
11 on the weight would tend to indicate that you might be,  
12 you know, adding, you know, the facts regarding those  
13 are really both. This is just another example of for  
14 thyroid endpoints also negative in the case.

15 For the fathead minnow you see again, you  
16 know, reduction in the reproduction which is shown but  
17 also the vitellogen response was a significant  
18 induction of vitellogen in males, all treatments, and  
19 in females at the high treatment also.

20 Switching over to the androgen pathway and  
21 looking at the assays associated which are AR binding,  
22 Hershberger, pubertal male and fish brain, they are  
23 binding again the test compounds applying to the  
24 androgen receptor. Hershberger is designed to detect  
25 chemicals that act through the air but to distinguish

1 the agonist and the antagonist and also incorporates  
2 the metabolic processes. Pubertal male and the fish  
3 detect the full androgen system, you know, having  
4 intact HPG axes.

5 Our first compound which wore the belt  
6 testosterone ordinarily a potent androgen in terms of  
7 what would be expected in terms of responses. A strong  
8 binder in binding, strong positive in the Hershberger  
9 indicate agonism. A positive in the pubertal male  
10 hitting on several of the key endpoints, the reclusive  
11 separation and tissue weights of various tissues and  
12 reduced things like testes and epididymis waste.

13 The fish brain was also positive for several  
14 of the endpoints and we'll go through these with some  
15 of the data from some example studies and at this point  
16 go on with this every day before that in the OECD  
17 Validation Program and again, important things like the  
18 ventral prostate, the seminal vesicles, the pelvic vc  
19 muscle complex, advanced penis toppers, all these were  
20 significantly affected at the higher doses.

21 In pubertal male at single dose accelerated  
22 reclusive separation, increased ventral prostate,  
23 seminal vesicles, and then a decrease in the air  
24 testes and air epididymis. In looking at the fish and  
25 one of the end points within the fish assay is one that



1 looks at secondary sex characteristics. In this case  
2 androgens will cause the emasculization or male  
3 secondary sex characteristics to be manifested in the  
4 female. The muscular tubules which are present in  
5 breeding male fathead minnows is a pronounced element  
6 of the organism. It doesn't occur in the females, but  
7 with the, it's controlled by the androgen. In the  
8 presence of methyl testosterone the female fish, you  
9 know, demonstrates, will display these secondary sex  
10 characteristics. The tubules will be manifest.

11 In this case also vitellogen was, was, was  
12 increased, you know, and testosterone's an androgen but  
13 it's an aromatizable androgen, and this slide shows  
14 that the aromatized methyl estradiol and estradiol, you  
15 know, binding curves are, are very close to each other,  
16 so that would give an indication that the androgen  
17 manifested its effect in terms of the androgenicity on  
18 the organism but also as it's converted, you know, will  
19 affect some of our estrogen end points at the same  
20 time.

21 And this is an example of the pronounced  
22 effect that this compound has on the reproduction in  
23 terms of the, you know, pre-exposure time and  
24 production of controls times zero, but at times zero,  
25 it, it looked of the treatment concentrations we had

1 virtually cessation of production of the eggs, so again  
2 an indication that these endocrine active material, you  
3 know, will affect the summary endpoint. It's not  
4 surprising, 'cause this is actually reproductive  
5 hormones entered as well to affect reproduction.

6 For one of our classic campaigns, the closest  
7 one has been the Roth study. It's a fungicide used on  
8 fruits, vegetables, variety of pesticide uses. It's a  
9 classic anti- androgen, inhibits the air dependent gene  
10 receptor expression in vivo. There are a variety of in  
11 vivo effects that have been studied in longer term  
12 studies, you know, as well, so we know or at least have  
13 a fair understanding of the compound in terms of how  
14 it's likely to affect us.

15 As far as the assays in the battery and how  
16 they respond, AR binding assays are somewhat equivocal  
17 in terms of a response and we can in some cases or at  
18 least it may be possible in others. The Hershberger  
19 was, you know, clear positive. The pubertal male  
20 positive again for multiple hits in terms of pop your  
21 goose off in separation and testes weigh, fish brain  
22 also key endpoints in terms of egg production, increase  
23 in some of the histological findings of the gonad and  
24 the ovary and reductions of male secondary sex  
25 characteristics.

1 The context here is in closing is also a  
2 metabolizable material and it's likely that within the  
3 AR binding especially for parent effects, the reasons  
4 that the parent is not as potent as some of the  
5 metabolites so when you get into the in vivo, you know,  
6 assay we're seeing much more upgrfts response. In the  
7 Hershberger, again, you know, the key point here is  
8 that you would be getting multiple hits across the  
9 various endpoints, you know, so that they corroborate  
10 and meet each other in terms of the action. In other  
11 assays like the pubertal we're also getting, you know,  
12 multiple hits, again corroborating the response as  
13 being, you know, anti-androgenic. You know, the fish  
14 again corroborating what we're seeing in terms of  
15 effects, summary effects in terms of fecundity, the  
16 outside atresia, increases in GSI, for vitellogen there  
17 was a increase in the females, tubules of slow results  
18 are reduced in, in, in males. And I think another  
19 context here in terms of how things are interpreted,  
20 you know, and part of the reason for having a taxonomic  
21 representation in terms of effects seen in the mammal,  
22 effects seen in the, in the fish would give good  
23 indication that this effect is likely going to be  
24 transferred throughout the kingdom and referred in  
25 universal in that context. If it was just within one

1 group versus another then that might raise the question  
2 as to whether it's going to be active in all particular  
3 morphology type levels.

4           The next examples that I deal with as  
5 fallacies as pesticides is in the area of commercial  
6 products causes a variety of male developmental effects  
7 characteristic of an anti-androgen, again in a variety  
8 of studies. In the assays we tested in terms of the  
9 battery for the air binding, this compound was a non-  
10 binder. From the Hershberger assay was negative, you  
11 know, in this in vivo system but in the pubertal male,  
12 again it was positive for responses to give an  
13 indication that the effect was likely referred more of  
14 an intact HPG, you know, for the, for the action to  
15 sort of be manifest, that the Hershberger is a little  
16 too narrow to pick that up, but for the pubertal male  
17 they were providing a variety of end points to boost  
18 the separation which is a key end point of that  
19 particular assay. Incidentally on the effects on  
20 reduction waste testes and the epididymis, which would  
21 also be indicative of anti-androgen type responses.

22           Moving to steroidogenesis the assays that are  
23 associated are at least informed from the compounds  
24 that have been in effect in this particular pathway,  
25 given the recombinant aromatase and then the H295R

1 which recombinant steroidogenesis. You know, these  
2 assays won't detect inhibition of aromatase and the  
3 steroidogenesis chemical that induced recombinant  
4 enzymes throughout this steroid syndrome.

5           The pubertal female takes chemicals that act  
6 on the estrogen system's adrenals. You know, pubertal  
7 male will affect chemicals that act on the Mayan  
8 androgen system and they know that as fish bait,  
9 similarly affected compounds that act on the estrogen  
10 egg systems. It's the main thing that interfered with  
11 steroid metabolism will likely manifest in one of those  
12 steroid controlled processes.

13           One compound that's been fairly well studied  
14 is Ki-comosol, swedisol and a foamal compound, its  
15 action is to inhibit steroid synthesis in fungi, but  
16 inhibits a variety of the cyclin p450 enzymes. It's  
17 also reported to induce progesterone production, and  
18 elements of it has inhibited testosterone and estrogen  
19 production.

20           In the assays and battery for aromatase,  
21 ketacosol was negative. For the recombinant  
22 steroidogenesis assay it was positive, recording a 90  
23 percent reduction of estrogen and testosterone in the  
24 in vitro system. In pubertal female it was positive  
25 with the effects seen on ovarian histopathology and on

1 fixed adrenal but no effect on vaginal. In the  
2 pubertal male was positive for delaying bruises and  
3 abrasion and for tissue weights and it reduced the  
4 testes growth.

5 In the fish brain, histopathology was the  
6 only positive with consistent positives in terms of  
7 providing cell proliferation. Just to go with the  
8 pubertal female, for vaginal opening it was negative.  
9 We had a significant, you know, effect on body weight  
10 gain which would give indication that we were right at  
11 maximum dose. In the other end points I could bring  
12 away, there was an increase in that to give an  
13 indication that it was a positive response. For the  
14 pubertal male more endpoints affected in terms of  
15 summary end points of reclusive separation, the  
16 seminal vesicles were all reduced and the testes and  
17 epididymis -- well, testes were reduced.

18 This is an example of the interstitial cell  
19 hyperplasia seen in the fish. I'm not sure that the  
20 pictures are that good, at least in terms of what the  
21 slides go, but the context if you can make it out is  
22 that the interstitial lighted cells are really small  
23 aggregates that are in between the seminal vesicles,  
24 but in the treatment these cell aggregates become much,  
25 much larger, you know, they do expand in the

1 interstitial spaces and you know, would be an  
2 indication that there is increased production of live  
3 cells which seek to compensate for production of  
4 additional stimuli.

5           Switching now to thyroid pathway, the three  
6 assays that are associated with this are the pubertal  
7 female, the pubertal male and amphibian metamorphosis,  
8 all with intact HPT.

9           One of the thyroid pathway compounds that we  
10 used across the, what is the chlore, it's a natural  
11 end result for chloric acid. It's used in solid rocket  
12 fuels, you know, it's also for treating thyroid  
13 disorders, it's also a constituent in some macro  
14 fertilizers which has led to a lot of contamination off  
15 site, but it's, the compound's a large one, it inhibits  
16 the thyroid gland's ability to absorb iodine. In the  
17 assays pubertal female was positive, increased flicker,  
18 cell height and color in the gland and decreased T 4  
19 and increased the TSH. A pubertal male, same story,  
20 the glandular pathology and then the decreased T4 and  
21 increased TSH. In amphibian metamorphosis we don't  
22 have the hormones as endpoints in assay but for the  
23 ones that we do include the pathology was similar to  
24 what was seen in the pubertals in terms of increased  
25 follicular cell height, reduced color area and then



1 for further endpoints that we do have in amphibian  
2 metamorphosis, there were developmental stage delays  
3 and morphology changes, this slide's to highlight that.  
4 In the amphibian metamorphosis again gland histology  
5 was the most sensitive of the end points, you know,  
6 where we, follicular cell height, color area, you know,  
7 increase in cell height, decrease in color area seen.  
8 The hymen length was reduced, the weight binding were  
9 increased and in terms of the, in terms of compound and  
10 developmental stage was significantly delayed but the  
11 root was seen only at the highest concentrations.

12           There's an example of the plant pathology.  
13 Again the control you have large colored areas and  
14 standard oswego cells, but within the treatment the  
15 follicular cell height increases and lose the color  
16 area and more pronounced at the increased dose and also  
17 causing somewhat of a plan I believe.

18           In the pubertal it's a similar story, here we  
19 have the bar graphs of the follicular cell increased  
20 with both the female and the male and the colored area  
21 decreased and then examples also of the gland histology  
22 which is, you know, a similar story that we saw with  
23 the amphibian gland.

24           Hormones let's go over, the T 4 is decreased  
25 in both male and female and the serum TSH increased in

1 both the male and female although the female seemed  
2 maybe a little bit more interested in a sense.

3           The next compound I want to talk about  
4 because it highlights one of the elements of an  
5 amphibian metamorphosis and this is hyponoic acid. This  
6 is a pharmaceutical that's used in radiologic imaging,  
7 inhibits the aromatase activity. We tested it in the  
8 amphibian assay and it inhibits the deonase which  
9 caused a dysynchronous development, a development  
10 stage that's determined by valuating specific  
11 developmental landmarks, which are spatially and  
12 temporally coordinated. The effects were as listed  
13 here. Retarded development, accelerated craniofacial  
14 tail development, decreased whole body length,  
15 decreased weight and effects on histological changes in  
16 the man where, you know, it varies, like some we've  
17 noted.

18           This is just from a, we were allowed to  
19 participate in an elaborate study of findings of  
20 asynchronous development, meaning different parts of  
21 the amphibian going through development, you know, were  
22 affected and this slide tries to demonstrate this in  
23 terms of typical control development and these stages  
24 that you can favor, you can favor are outlined stage  
25 specific classification when you process for the

1 various stages that that form of development you both  
2 grew and in stages, you know, 59, 60, 61 you can see  
3 kind of a progression where you, you know, the  
4 craniofacial development, you know, changes, and actual  
5 head size reduces, but you see a lot more development  
6 as you move through progressions, the tail would be  
7 reserved and the limbs become more developed but in  
8 the typical IOP treatment situation the head fall is in  
9 a confused state in terms of development, in terms of a  
10 tail at the very advanced stage 63, the limbs are in  
11 kind of a retarded, stage 59, the head in somewhat of  
12 an advanced 62 so the context is that the peripheral  
13 tissue response wherever the deonase occurs is causing  
14 a developmental modification. In this case the  
15 amphibian assay is the only one assay that exists with  
16 an end point that would relate to the peripheral tissue  
17 responses or at least the deonase in peripheral  
18 tissue. So the context of that assay is one that would  
19 need to be, you know, present to be able to pick up  
20 those kinds of activities.

21 I'm just going to go through some kind of  
22 summaries now in terms of the strength of the battery  
23 and its ability to detect. And this slide's a little  
24 different from the original package that we have and I  
25 think that everybody has, it should have been

1 distributed, a replacement slide, for slide 60 where  
2 what we've done is just added which assays, the  
3 previous slide just has several assays, you know,  
4 given an activity but here we're trying to spell out  
5 the specific assays. For estrogenic activity, again,  
6 the idea of binding, we have transcriptional  
7 activation, which will cover the, you know, binding  
8 and inform whether we got agonists, for 3000  
9 uterotrophic female pubertal and the fish covering the  
10 end points and taxonomy separation and also the  
11 metabolism in the anti estrogenic activity we've got  
12 neo binding but in the in vivo just the female pubertal  
13 and the picture will cover that activity and the  
14 taxonomic, you know, range. For androgenic activity we  
15 have in vitro and Hershberger and the intact HPGs, the  
16 male pubertal in fish and the same for the anti-  
17 androgens. And the population that's steroidogenesis,  
18 we have the H295R, male female pubertals and fish. I  
19 mean, what basis is the story the tail end of the  
20 steroidogenesis?

21           Altered effects on the hypothallic pituitary  
22 function and this would include HPG and HPT where  
23 appropriate and male/female pupils come from cobalt HPG  
24 to fish's HPG and then amphibian metamorphosis is the  
25 HP as it relates to the HPT.

1 For antithyroid activity we have both the  
2 male female pubertal and the amphibian metamorphosis.

3 For thyrominetic activities, you know, it has  
4 always been demonstrated as amphibian metamorphosis and  
5 as we mentioned the perfect example of that he for  
6 those peripheral tissues and responses and giving them  
7 rough effects.

8 In interpreting the battery, as was mentioned  
9 by Gary in his presentation, I mean, using the weight  
10 of evidence includes professional judgment, you know,  
11 some end points more diagnostic specific than others  
12 and, and really it's the weight of various effects seen  
13 in multiple endpoints and across multiple assays that  
14 carry the most weight. We're looking for that  
15 confirmation of corroboration across the assays and two  
16 possible interpretational outcomes, either the  
17 potential for the activity on estrogen action  
18 hormones, that would require some further analysis to  
19 the Tier 2 family of the patient or we can interpret  
20 that there's low and no potential for EAT activity so  
21 that the compound can be, you know, pushed aside  
22 instead of somewhat harping on it.

23 In summary, your multiple assays are required  
24 to comprehensively screen estrogens and androgens, the  
25 thyroid hormone systems. The in vivo assays are good

1 for well understood mechanisms like simplifying in vivo  
2 assays, in vivo assays with intact HBG, HPT axis are  
3 good for efficiently screening complex processes,  
4 multiple taxa and multiple modes of action end points  
5 provide a range of metabolism and corroboration that  
6 would be needed in interpreting, you know, that the  
7 effects are likely manifested through endocrine  
8 systems. The complete battery is needed to support a  
9 weight of the evidence finding something lower, low  
10 potential for EHE activities.

11           The next two slides pretty just repeat the  
12 third question which I think will be the subject for  
13 the next day, but the first charge question really gets  
14 at, you know, how effective is the battery at covering  
15 the extra damage in the thyroid system and then the  
16 second charge question where it gets at, you know, how  
17 well the battery works as integrated in a system in  
18 terms of what combinations are likely to be considered  
19 for that and so with that I thank the panel for their  
20 attention and try to answer any qualification questions  
21 you have at this time.

22           **DR. HEERINGA:** I thank Dr Touart, but  
23 first of all I'd like to commend both you and Gary Timm  
24 for very efficient presentations and I think made very  
25 good use of our time, well organized, thank you very

1 much. What I'd like to do is, I'd like to take a break  
2 and then return for questions from the panel so that we  
3 have a little bit of a chance to for people to get up  
4 and have a chance to stretch and we'll return and then  
5 we'll take questions on your presentations from the  
6 panel.

7 For the audience at large, this is a  
8 floating agenda and I think we're moving right along, I  
9 think we will go into the period of public comment so  
10 those of you who are prepared for public comment I'm  
11 not sure whether we'll start before the noon hour but  
12 we'll certainly start first thing after the lunch hour  
13 for public comment but when we return from the fifteen  
14 minute break, I have 10:36 so let's come back here at  
15 why don't we say five minutes of eleven and we'll  
16 return to some questions on the scientific  
17 presentations. Thank you very much.

18 (WHEREUPON, a brief recess was taken.)

19 DR. HEERINGA: Okay, welcome back,  
20 everyone. I'd like to again welcome you back to the  
21 second half of our first morning session, the meeting  
22 of the FIFRA Science Advisory Panel and the topic of  
23 the Endocrine Disrupter Screening Program Proposed Tier  
24 1 Screening Battery. At this point we have heard and  
25 seen presentations from Gary Timm and Dr. Les Touart



1 and we have reached a point where I'd like to open it  
2 up to the panel members for questions of clarification  
3 for Dr. Touart or Gary Timm with regard to their  
4 presentations or any of the materials that were in the  
5 technical report. Dr. Kullman.

6 **DR. KULLMAN:** Seth Kullman. Dr Touart,  
7 you had mentioned the weight of the evidence several  
8 times and it appears that several compounds have slight  
9 differences from their modalities and was curious if  
10 you could expand a little bit more on the weight of the  
11 evidence process.

12 **DR. TOUART:** I'll try to expand a little  
13 bit. I think the context of the weight of the evidence  
14 again in terms of multiple end points within some of  
15 the apical assays, I think some of the in vitros or  
16 Uterotrophic and Hershberger have, have maybe fewer,  
17 you know, end points to consider but with the regular  
18 assays there are a variety of end points that touch on,  
19 you know, the range within say an HPG where you may  
20 have estrogenic, androgenic or even thyroid endpoints  
21 that could be affected at the same time. The context  
22 of the battery isn't to identify a specific mode of  
23 action but to be able to detect, you know, an activity  
24 if that mode of action exists, you know, so that if we  
25 see effects in multiple endpoints and in multiple

1 assays especially across various taxa in terms of the  
2 rodent and, and fish or frog, the indication would be  
3 that this is a potential, you know, for disrupting  
4 those types of systems whether it's the, you know, HPG,  
5 HPT or, you know, for some compounds maybe both in  
6 terms and by having multiple endpoints and multiple  
7 facts I think that the weight of the evidence would  
8 give an indication that that's real as opposed to if  
9 only, you know, one end point and one assay were to  
10 like I say you might get a receptor binding in the ER  
11 binding assay but everything else the transcription  
12 activation's negative, the, say, uterotrophic is  
13 negative, the pubertal, you know, female's negative and  
14 the fish repro is negative. The indications would be  
15 that while it may have some binding affinity, but  
16 there's not a potential to disrupt the system, but if  
17 you see effects, you know, in multiple assays then I  
18 think you have to consider. In a, in a given assay  
19 you'll see whether it's a pubertal or fish assay if you  
20 have a summary end point that's affected and it's  
21 corroborated by other end points in that assay then I  
22 think you can't necessarily ignore that, say you have  
23 the fish you have vitellagenic induction, you have  
24 gonadal, you know, pathology and you've got  
25 reproduction error, I think the context of that path

1 used even if you didn't see an effect in the pubertal  
2 or you didn't have corroborating evidence in the in  
3 vitro assay you'd still have to think, well, there's a  
4 potential, the context of that potential as to whether  
5 it is universal, comes in all vertebrates or whether it  
6 might be unique to fish or non-mammalian systems would  
7 be something that we'd have to kind of look and see,  
8 well, what evidence did you have emanating from the  
9 rodent studies.

10 **DR. KULLMAN:** Will this remain a  
11 qualitative assessment or will you try to make it a  
12 quantitative assessment?

13 **DR. TOUART:** The purpose of the Tier 1  
14 is to be qualitative just to indicate a potential. The  
15 purpose of the Tier 2 is to do the actual concentration  
16 response, the dose response information and to really  
17 assess the adverse consequences, so once we see that  
18 there's a potential then we will go into the Tier 2  
19 tests until, to try to get the quantification of that  
20 particular event.

21 **DR. HEERINGA:** Before we turn to the  
22 next question I was a little out of order. I wanted  
23 to make sure Dr. Furlow's arrived and give him a chance  
24 to introduce himself. David.

25 **DR. FURLOW** David Furlow, UC Davis by

1 way of Los Vegas and Atlanta, my laboratory focus is on  
2 thyroid hormone regulation of amphibian metamorphosis  
3 but also corticosteroid regulation of muscle mass in  
4 mammals as well so kind of multi species and multi  
5 hormones.

6 **DR. HEERINGA:** Thank you very much,  
7 David. Dr. Bucher

8 **DR. BUCHER:** John Bucher, I was  
9 wondering if you would just spend a minute talking  
10 about issues related to the guidance that EPA will give  
11 for dose selection and concentration selections for the  
12 in vitro and in vivo assays, general terms.

13 **DR. TIMM:** For the in vitro assays for  
14 the most part, John, we have specified a top dose, a  
15 limit dose and so for the binding assays, for the  
16 aromatase assays, for instance, and also I think for  
17 the H295R we would pick, go one millimole or perhaps  
18 ten micromolars as the top dose and run doses down  
19 probably logarithmically and that would be for the  
20 first run and then for the second run they could tailor  
21 things based upon what they saw. I'll let Les talk  
22 about the in vivo.

23 **DR. TOUART:** I think the context in the  
24 in vivos in terms like of our studies the context is  
25 I'm trying to establish the maximum power eight dose

1 and that would usually be defined as like a dose that  
2 doesn't affect less than ten percent weight reduction  
3 in the fish and frog. The context is that we want to  
4 evaluate a dose that's below a, you know, toxic level,  
5 generally using like a mentality type of end point if  
6 we have LC50, LD50 type of information, we'd be  
7 stepping down, you know, from that to get to a  
8 concentration where we would not likely see overt  
9 toxicities. One of the contexts of having multiple  
10 doses in the screens again because they're somewhat  
11 more qualitative and quantitative but having multiple  
12 doses allows us if the high dose, if we do get  
13 mortalities or other overt signs of toxicity than to  
14 lure concentrations but hopefully, you know, still  
15 suffice to be able to identify that we touched I guess  
16 concentrations that would still be relevant and that  
17 the effects we would see would be more likely endocrine  
18 mediated than non. I think the, part of that thinking  
19 is that for those materials where we are within toxic  
20 range we can at least can have any kind of responses  
21 and affect any of the endocrine endpoints but also the  
22 contexts that our other more traditional toxicity  
23 tests, you know, get the knowledge from a hazard  
24 assessment risk assessment perspective would be able to  
25 deal with those materials very effectively for the

1 purpose of, you know, dealing with endocrine  
2 disruption, and that context would be that these will  
3 likely affect that otherwise would be missed or at  
4 least be more pernicious in terms of the effects on  
5 growth development or reproduction.

6 **DR. HEERINGA:** Dr. Vandenberg and then  
7 Dr. Chambers.

8 **DR. VANDENBERGH:** John Vandenberg, I  
9 wonder -- well, I understand that it would be difficult  
10 to add any new protocols to the testing procedure at  
11 this point but I wonder about within the ones that have  
12 already been identified here, is there flexibility as  
13 far as the panel is concerned about tweaking any of  
14 the protocols or eliminating any aspects of them?

15 **DR. TOUART:** I guess from my perspective  
16 I mean that, we're open to that kind of advice or  
17 suggestion but I think the context of if there are  
18 unnecessary end points or end points that might  
19 otherwise be tracked or overload a particular assay,  
20 the context of you need additions I think those are  
21 possible as well as long, again, you know, it's the  
22 context of the analogy of the Christmas tree. You  
23 don't to have too many ornaments, you know, or it will  
24 topple over but you still want to have enough and also  
25 we want to be able to make use as much as possible of

1 the animals that we utilize so those end points you  
2 glean as much information for the use of the animal we  
3 want to make sure that we captured every piece of  
4 information that we can. In the context of other  
5 modifications in our view point what we're trying to do  
6 is establish some kind of a basis that in terms of a  
7 battery and any improvements, you know, modifications  
8 of an assay or other assays these can be folded in,  
9 you know, some of these may be considered like  
10 performance based type of a concept where if you have  
11 an assay like a different transcriptional activation  
12 type assay that may exist or a different, you know,  
13 recombinant cell line or something like that, you know,  
14 but if it performs the same function, you know, as  
15 long as it can demonstrate that it gives the same  
16 information or perhaps better information so much the  
17 better and the same for the in vivo assays if there's a  
18 way of getting the same information and it will use  
19 those, you've kind of established this kind of a  
20 reference then anything else that comes along that's as  
21 good or better or gives the same information quicker,  
22 cheaper, whatever, then that would also be, you know,  
23 up for consideration. It's just I think right now we're  
24 limited in what we see and if the panel's aware of some  
25 things that are probably up to speed or ready for prime





1 time then we're willing to, you know, consider those as  
2 well.

3 **DR. TIMM:** Just one add on note. The  
4 validation requirement is a substantial one and so  
5 there's probably a lot of stuff out there, there may be  
6 things that might even be better than what we have but  
7 they haven't been validated, at least for right now we  
8 can't use them, we would have to go through a  
9 validation process and of course we're working with  
10 OEC, OECD to validate some other things that are not  
11 quite ready yet.

12 **DR. VANDENBERGH:** May I follow up  
13 quickly, is there any plan for review of the program at  
14 some intervals in the future?

15 **DR. TIMM:** I'll be happy to speak to  
16 that point. As part of that review back in 1999 by the  
17 SAP, they recommended a number of things, they said  
18 this was a really ambitious program and they said, you  
19 know, don't just go full boar, that you should take  
20 fifty to a hundred chemicals and then full stop, look  
21 at what results you've obtained on those fifty to a  
22 hundred chemicals and re-evaluate your battery in light  
23 of that information and prune it if there's some things  
24 in there that provide unnecessary duplication,  
25 substitute some things out if there's better technology

1 that has been validated for some assays but that's  
2 exactly what we intend to do.

3 **DR. HEERINGA:** Dr. Chambers?

4 **DR. CHAMBERS:** I'd like to follow up on  
5 Dr. Bucher's question of a minute ago, Mr. Timm. The  
6 limit doses that you're talking about in the in vitro  
7 assays, are those based on toxicity levels or  
8 solubilities or anything like that or just arbitrary  
9 levels?

10 **DR. TIMM:** They were basically consensus  
11 levels but that's the idea that you would run it first  
12 time and go up to the limit dose if you could. But you  
13 clearly have to look for precipitate, make sure that in  
14 fact you're not exceeding the limits of solubility.  
15 Then if it's a cell based assay you're also interested  
16 in cytotoxicity so that would also limit your  
17 concentration so we don't expect the assay to always be  
18 run up to the limit dose but that's the first thing to  
19 start with, check for solubility, check for  
20 cytotoxicity if that's applicable and then make your  
21 second and third runs accordingly.

22 **DR. HEERINGA:** Yes, Dr. Lasley.

23 **DR. LASLEY:** Is there accommodation or  
24 flexibility for emerging new mechanisms of action in  
25 terms of endocrine disruption?

1 **DR. TIMM:** Not on this seventy three  
2 chemicals but down the road, clearly what EDSTAC said  
3 is hey, this is a rapidly changing science, that EPA  
4 will need to look at other mechanisms of action, other  
5 hormone systems in the future.

6 **DR. LASLEY:** What about hormones that  
7 interact with your EAT hormones, are they to be  
8 included now or would you delay that?

9 **DR. TIMM:** We are pretty well set on the  
10 battery of assays that we have and we really, you know,  
11 we can't add to those, we've got deadlines to get the  
12 program going, we've got the battery we've proposed, we  
13 would like your comments on that and as Les indicated,  
14 you know, if there are endpoints within assays that you  
15 don't think really add to the value of the battery or  
16 add to that value of that assay, we would like your  
17 recommendations on those. If you think that among the  
18 suite of things that we have, we should put more in,  
19 that there's something there that's final, I want to  
20 hear that. If you think that we've got needless  
21 redundancy and some assays should come out then we want  
22 to hear that, but it's, it's really focused on the  
23 battery we proposed.

24 **DR. LASLEY:** Still what I get from that  
25 is this is a reductionist point of view; in other

1 words you would tolerate reducing your battery but not  
2 adding to it?

3 **DR. TIMM:** What you could certainly  
4 recommend is some other areas but they would be really  
5 recommendations for research. At this point they would  
6 not be recommendations for inclusion in the battery at  
7 this time.

8 **DR. HEERINGA:** Dr. Cooke.

9 **DR. COOKE:** Joe Cooke, what combination  
10 of positive results would trigger a Tier 2 testing?

11 **DR. TOUART:** Again, the way of the  
12 others and one could go through lots of permutations, I  
13 think one would have to look at the nature of which  
14 assays were positive, if it's a single assay, you know,  
15 the severity or the magnitude of the change in the end  
16 points that were associated and again which assay I  
17 think for the apical assays, you know, one's going to  
18 place more weight on those than one places say on the  
19 in vitro assays. I think the in vivo tend to trump in  
20 vitro if in that context but to try to identify like if  
21 a single end point it is affected, you know, if it's a  
22 severe response I think it may warrant, you know, some  
23 further investigation. Whether, you know, that's a  
24 clear trigger for Tier 2 or just, you know, something  
25 else is maybe something that could be debated but most

1 cases an experience that we have is for some of the  
2 more significant end points if those are the type that  
3 there's usually corroborating information and other end  
4 points to suggest that those are real benefits, not  
5 just a, you know, say a false positive, you know, kind  
6 of a context and that's part of the strength of having  
7 multiple assays and stuff, but I think if it's a single  
8 end point and a single assay one would have to look at  
9 that with a little more caution than when one's looking  
10 at multiple hits in multiple assays.

11 **DR. HEERINGA:** Gary Timm?

12 **DR. TIMM:** Yes, if I may add, in the,  
13 some of the examples that Les ran through in his talk  
14 what you could see is some characteristics that  
15 indicated, gee, this chemical needs because it was  
16 negative in vitro but it was positive in vivo assays,  
17 it clearly needs metabolism to be active, it's one of  
18 the metabolites, it's active, so, you know, you,  
19 there's no way to assign points to assays and add up  
20 the points and magically if you hit a certain number it  
21 goes to Tier 2. It, you have to use judgment and part  
22 of the reason for having the battery is that you get a  
23 picture as to what's going on and you can really  
24 hypothesize what sort of stuff might be happening here  
25 and looking through mammalian assays, looking at your

1 fish assays, looking at your in vitro assays decide  
2 whether in fact you've got something that's a concern  
3 or it's not a concern.

4 **DR. HEERINGA:** Dr. Isom.

5 **DR. ISOM:** When we look at the battery  
6 and the objective that you state is to identify the  
7 potential and not to I guess elucidate mechanism. And  
8 when you look at the total battery, the in vitro  
9 assay's a little more mechanistic I guess you could say  
10 and the more complex in vivo assays will give you the  
11 same information plus additional information so I'm a  
12 little confused then why we have that overlap and why  
13 it is stated that we're not interested in mechanism if  
14 you just pointed out by running the battery we'll have  
15 some idea of the mechanism.

16 **DR. TIMM:** I think we're interested in  
17 mechanism, but I don't think that one can conclude that  
18 because you've seen say estrogen receptor binding that  
19 that is necessarily the mechanism by which a chemical  
20 is acting. I remember a case, a number of years ago,  
21 where yes, it was an estrogen receptor binder but in  
22 fact they found out when they ran some more experiments  
23 that indeed it also regulated aromatase. Now with our  
24 Aromatase, recombinant aromatase inhibition assay we're  
25 never going to see that. Hopefully we would see that

1 in the H295R and I think it would expect to see that  
2 but to really nail down mechanism you really have to  
3 have a...you have to formulate a hypothesis which I  
4 think you could with the assays we have but you need to  
5 confirm that hypothesis in some additional follow up  
6 experimentally designed studies, sometimes this will  
7 give you the mechanism but I don't think you can always  
8 guarantee that what you see is going to be conclusive  
9 proof of, that that's the mechanism of which it  
10 operates.

11 **DR. HEERINGA:** Dr. Brown.

12 **DR. BROWN:** Terry Brown, I just have a  
13 question about the practical implication of the assays,  
14 how many laboratories will be running these assays, how  
15 will they be selected, what kinds of, you know,  
16 expertise will be required within various laboratories  
17 to evaluate particularly in the in vivo assays where  
18 you have a constellation of end points where many of  
19 them may lend themselves to different interpretations  
20 based on the expertise of the individuals who are  
21 looking at the histology or other aspects of the  
22 assays.

23 **DR. TIMM:** Histology may be one of the  
24 limiting factors here. Of course selection of the  
25 laboratories will be the responsibility of the



1 regulated industry because what these test orders do is  
2 that they will require the industry to test compounds  
3 and typically several companies who manufacture or who  
4 register a chemical as a pesticide will band together  
5 to jointly sponsor the testing, it could be done in  
6 their own in-house laboratories, if one of them has a  
7 toxicology laboratory that can do these tests or they  
8 could go out to the commercial sector and use one of  
9 the commercial laboratories. One of the things that we  
10 plan on doing is to develop some data to answer your  
11 question because we have not yet since we, since only  
12 recently the protocols were even nailed down we have  
13 not gone out and done a survey to see how many  
14 laboratories there are but that's something we clearly  
15 want to do.

16 **DR. HEERINGA:** Dr. Touart.

17 DR. TOUART Just a follow up I think one  
18 of the elements of the validation was to evaluate  
19 transferability of protocols and part of doing it in  
20 the laboratory investigations were to collect  
21 laboratories at least in employee laboratories and with  
22 the protocols to determine, you know, how well they  
23 were able to follow that and then to adjust the  
24 guidance in that context. In some cases, for some of  
25 the endpoints that are a little bit more, I guess

difficult than others like histopathology, I mean, we went to great efforts to develop guidance documents to explain things, you know, very, very clearly so I think there's a lot of guidance, but I think as Jerry points out there's still questions in terms of the numbers of laboratories and the lab capacity for doing some of the, you know, the assays that we're talking about in terms of the number of compounds in the first group.

**DR. HEERINGA:** Dr. Furlow and then Dr. Delclose.

**DR. FURLOW:** It's just to follow up on that, so one of the inter-laboratory validation concerns at least I think in the pubertal assay was perhaps measurements of TSH for instance and each lab may use a different kit, et cetera, and the EPA in the documentation said that you guys didn't feel that that was your place or in your purview to sort of be the in house hormone assay department, but couldn't there be some contract lab that's designated that could in fact coordinate these things so each lab isn't doing all those assays?

**DR. TOUART:** I'm not sure if there would be a single lab say that would be given sometimes a prize of being able to manage all that but I think that the context for the assays and some of those types of

1 end points is to have some performance material in  
2 terms of what one's expected so if one uses a  
3 particular type of hormone kit versus somebody else  
4 that they're still able to be able to differentiate,  
5 you know, and to demonstrate that kind of context. If  
6 in terms of lab capacity situation, if the industry  
7 wants to double up or at least to have specialized  
8 centers that can do work, I guess that's something that  
9 would be within their volition to try and do, but I  
10 think from the context what we want to try to do is  
11 provide test method guidance and performance criteria  
12 for those methods so that those would be, you know, we  
13 would have confidence that they would be conducted and  
14 be acceptable when the data presented.

15 **DR. HEERINGA:** Gary Timm.

16 **DR. TIMM:** In addition, I mean  
17 government is supposedly in the business of breaking up  
18 monopolies and not creating them so to specify that  
19 someone must use a particular kit is something we  
20 wouldn't do and OECD under their guidelines clearly  
21 would not do that as well so I think that's the reason  
22 Les says the approach we would take would be to try to  
23 set the performance criteria so that we might even, if  
24 a validation were conducted by someone and a number of  
25 different kits met the criteria, certainly there's a

1 way to inform people that these have met it and so that  
2 these they can choose from but clearly we would not  
3 specify one particular approach.

4 **DR. HEERINGA:** Dr. Delclose.

5 **DR. DELCLOSE:** Barry Delclose, I was  
6 just wondering if you envision this is this going to be  
7 a yes or no, goes through Tier 1 and you know, send it  
8 to heaven or to hell or is there a purgatory so that if  
9 you got you say in vivo assays would trump in vitro, if  
10 there were, say, two in vitro assays are positive and  
11 all of your in vivo assays are negative, are you just  
12 going to stop there and say, well, it looks like this  
13 is probably not a concern or a low level concern. Would  
14 you be concerned about things like thorough  
15 characterization of that metabolic profile in young  
16 animals, for example, maybe there's a difference in the  
17 way the compounds metabolize so I know you made mention  
18 in the in utero fly-tational that there's a possible  
19 Tier 1 point five, is there envisioned for something  
20 like that? You've got enough concern here. I would  
21 imagine that the industry would do that anyway, would  
22 look into it further if that kind of situation came out  
23 in research.

24 **DR. TIMM:** We won't have a real Tier 1.5  
25 but I suspect if there's a real conundrum that as you

1 said industry will probably conduct a special study  
2 probably in consultation with us if they can formulate  
3 a hypothesis of what might be going on and can design  
4 such a study that would be probably something that we  
5 would both be interested in.

6 **DR. HEERINGA:** Dr. Touart.

7 **DR. TOUART:** Just a follow up. Just  
8 normal regulatory process, you know, there is the  
9 ability for industry to do like a rebuttal or  
10 something, I mean if we come in with our interpretation  
11 of the Tier 1 say, you know, this triggers Tier 2 but  
12 the industry would have a different perspective, they  
13 could provide some information or evidence to indicate  
14 why, you know, they felt that we over interpreted or  
15 misinterpreted, you know, the information so there's  
16 that potential context but again I would hope that the  
17 logic and rationale that we would be using in our  
18 weight of the evidence and the findings that we would  
19 have would be sufficiently supportive in the case that  
20 that would kind of establish what we need to be doing  
21 next.

22 **DR. HEERINGA;** Other questions from  
23 panel members with regard to the presentation. Dr.  
24 Denver?

25 **DR. DENVER:** I have a couple of

1 questions. Actually the one relates to a follow up of  
2 the question that was just asked and that is being able  
3 to detect endocrine disruption at early developmental  
4 stages so early development tends to be very sensitive  
5 to disruption and I don't know that any of these assays  
6 are specifically designed to address that question. If  
7 that's been considered.

8 **DR. TIMM:** Back when EDSTAC was  
9 deliberating, one of the things that they talked about  
10 to use low doses, they talked about in utero or in ovo  
11 exposures and of course there was always the desire to  
12 have that in utero or in ovo part of that assay being a  
13 screen and they don't look much like screens, they're,  
14 to have enough end points in there to do the kind of  
15 job you want they become rather laborious and  
16 complicated but also the consensus of the committee was  
17 that you probably will not have an endocrine disrupter  
18 that does something only in the developing animal and  
19 shows no signs at all at puberty or so the idea was  
20 that you would have these higher dose level studies  
21 performed in the pubertal animal or in the fish repro,  
22 I mean you do really have here a different life  
23 exposure stage in the fish reproductive study so that  
24 by that combination the thought is that you would catch  
25 most everything of real interest.

1 **DR. DENVER:** Well, I think that I would  
2 beg to differ with that characterization because I  
3 think that it's clear that early developmental stages  
4 can be perhaps more sensitive to endocrine disruption  
5 than pubertal stages. Also it's also important to  
6 point out that the actions of hormones can differ  
7 dramatically between early developmental stages and  
8 later stages. In fact you can have just the opposite  
9 effects of some hormones during early stages versus  
10 later stages.

11 **DR. TIMM:** I would not dispute either of  
12 the two points that you made. I guess that what I  
13 would still say is that how likely is it that you're  
14 going to have an effect of a compound on development  
15 where you see absolutely nothing in any of the other  
16 assays in the battery. There may be such a compound.  
17 If you know of one, we'd like to know about it, but  
18 that is our... that's currently our view based upon  
19 what we've seen.

20 **DR. HEERINGA:** Let's be sure we don't  
21 drift into our recommendation from the discussion but  
22 go ahead.

23 **DR. DENVER:** Yeah. Well, I guess I'm  
24 just trying to understand how if one has say a positive  
25 result in an in vitro assay but all negative results in



1 in vivo assay, then does one consider that that could  
2 have some effect say at a different developmental  
3 stage? I think that was the question that was posed  
4 here earlier, right, so would an in vitro result but  
5 not an in vivo result trigger further investigation of  
6 the potential?

7 **DR. TIMM:** I guess the... you know, we  
8 tend to look at statistical significance as a yes/no,  
9 and maybe in this case what one would want to look at  
10 is look at all your end points, you've got a, some very  
11 strong signals in vitro but you had some end points  
12 that came up in vivo and they were .08, didn't make  
13 .05, maybe you'd say hey, there is really something  
14 going on here, but in general if you can't get anything  
15 in vitro or in vivo rather in these assays, why would  
16 you expect to see something in vivo in the two  
17 generation assay for instance.

18 **DR. HEERINGA:** Dr. Touart had some  
19 contributions.

20 **DR. TOUART:** I just, this was a follow  
21 up to the earlier question in terms of early  
22 development in context as far as a component like that  
23 in the battery but typically what I think what can  
24 occur with changes or exposures that may occur like in  
25 ovo or embryo it may not be manifest until that

1 individual reaches adulthood or maturity and the  
2 context of that is you're talking a much longer term  
3 assay than even some of our apical assays already which  
4 twenty one days or so can be considered a pretty long  
5 time for a screen and so that's the context of  
6 considering and we do have some early development but  
7 they're not earlier, I mean it's like pro metamorphosis  
8 in amphibians but again those are for thyroid endpoints  
9 not for other, you know, reproductive type effects.  
10 There is a component in the fish short term  
11 reproduction assay if you were to collect the eggs that  
12 you're counting in terms of what's being produced,  
13 those can be kept and hatched and end points collected  
14 which would be really effectively the beginning of your  
15 mostly generational task but we felt that from the  
16 screening context as Gary pointed out, that for most of  
17 the kinds of compounds that we are aware of we still  
18 are able to get some, you know, catch in terms of the  
19 assays that present but I think again it would be, it  
20 would be difficult for us, it's just a positive in the  
21 in vitro and all the in vivos were negative in kind of  
22 a firm negative in context to think well, to go into a  
23 multi generational study again at the screens are  
24 tested at fairly high levels, you know, the context  
25 that these are lucky to, you know, still manifest it

would be a difficult sell for us.

**DR. HEERINGA:** Dr. Denver.

**DR. DENVER:** So my other question goes to the broad goals of the screen which are to identify compounds that disrupt the endocrine system not only in humans but also in wildlife, and in some cases those goals appear to be separable, for example, in case of the fish reproduction screening assay I think you mentioned that that was intended to be specific to fish, although it can identify some estrogenic or potentially anti-androgenic compounds but what I was curious about is the amphibian metamorphosis assay considered to be an assay that would identify compounds that would affect amphibia and how would the EPA use the information from all these different assays to assess the risk to humans versus wildlife or are those two considered together?

**DR. HEERINGA:** Dr. Touart?

**DR. TOUART:** I didn't mean to imply that the fish is for fish and that the frogs were for frogs, I think that the context of these are established kind of the bookends of the file and the fish and form what we see on the mammalian side as well as on the mammalian side when flora when we see in the fish. If we get corroboration between the fish and rodent or the

1 frog and rodent I think the indication is that this is  
2 something that is more, you know, universally manifest  
3 through vertebrates and we would anticipate that birds  
4 or reptiles or really any, any class of bird primate or  
5 what not would, would likely also be affected if we see  
6 in just one if just the rodent is positive but we don't  
7 see a positive in the fish say for compound, or in the  
8 frog the context it could be a metabolic difference  
9 that could explain that in terms of the mammal couldn't  
10 metabolize it into an active form and vice versa if the  
11 situation was reversed in the fish, so those are some  
12 things that we'd have to take a look at but if  
13 the...there were several end points that were affected  
14 within a given group but we didn't see it in the other  
15 taxonomic group, then that potentially could affect how  
16 we treated the Tier 2s in terms of which group might  
17 get looked at but the general sense would be that it  
18 would have been flagged as a potential and given that  
19 we have different life stages in terms of a pubertal  
20 rodent versus a say a reproducing adult in the fish or  
21 larvae in the frog. The indications are that a  
22 different life stage may also be affected, so the fish  
23 and frogs are to work in combination with the mammalian  
24 assays and we're really not considering them a mammal,  
25 the fish, or the frog, they're just sort of models that

1 are being utilized in interpreting and that some of  
2 those models have... give us better insight and better  
3 resolution for effects that may be occurring in one  
4 case versus another.

5 **DR. HEERINGA:** Dr. Zoeller

6 **DR. ZOELLER:** Tom Zoeller. To maybe  
7 rephrase that a little bit is Tier 2 tailored to the  
8 specific kind of profile of effects that you see in  
9 Tier 1 or if Tier 2 is triggered it's the entire tier?

10 **DR. TOUART:** Well, most likely it would  
11 be the entire Tier 2 because for a lot of this there's  
12 an exposure component and the context is that if  
13 everybody's exposed then there's a potential we would  
14 only take a look at if there was exposure information  
15 did it indicate that the particular compound because of  
16 its manufacturing or use, there's really just a subset  
17 that's exposed, maybe it's just, you know, humans in  
18 an indoor type situation and there's not anticipation  
19 for fish or wildlife that would have any substantial  
20 exposures then be retained just on the mammalian side  
21 and vice versa if a material's released, but, but it's  
22 hard to contemplate a particular compound if it's out,  
23 it's out, everybody's going to get exposed in some  
24 fashion in terms of if it gets into the water fish  
25 would have it, the fish would be up the food chains or

1 what not, so other wildlife as well as humans would be  
2 affected in that context. I mean, the drinking water  
3 is coming from, you know, those sources of supplies  
4 would be of concern so there's, you know, there's a  
5 potential would be more likely is that one might focus  
6 on given end points in the Tier 2 to say well,  
7 everything seems to be indicating that this is a potent  
8 estrogenic type compound, so we want to pay more  
9 attention to those modalities and ramifications that  
10 would be more related to estrogen and maybe not spend  
11 as much time on something say like thyroid type end  
12 point necessarily, the context being that if you have  
13 limited choices in terms of what assays you're doing,  
14 whether you're going to look for a given hormonal  
15 measure or a histopathology type measure you may want  
16 to make some of those type of choices based upon what  
17 kind of mechanism you think might be involved, but  
18 again the Tier 1s aren't really defined mechanisms, in  
19 some cases we've got stronger indication than in others  
20 but I think it would still be a little bit dangerous  
21 for us to try to form any conclusions from the Tier 1  
22 data per se if that helps.

23 **DR. HEERINGA:** Other questions of  
24 clarification from the panel. Dr. Delclose?

25 **DR. DELCLOSE:** Barry Delclose, this is a

1 pretty simple question I think. In the OECD guideline  
2 for the uterotrophic assay it gives a choice between  
3 the immature and the castrate, and indicates that the  
4 immature is preferred for animal welfare concerns, it  
5 also indicates that it's responsive perhaps less  
6 sensitive but the response is to a broader range of end  
7 points because of the HPG acts as an impact, but that's  
8 not listed among your HPG responsive assays.

9 **DR. TIMM:** I think if we were having the  
10 uterotrophic done for us, we would probably request  
11 that it be done using the subcutaneous route in an  
12 animal, however if a uterotrophic assay exists, and  
13 it's done according to the OECD guidelines we certainly  
14 would accept those data. There's the Mutual Acceptance  
15 of Data Treaty that we are party to back in 1983 and so  
16 we would use those data and make an evaluation on that  
17 basis.

18 **DR. DELCLOSE:** So your guideline is not,  
19 is not necessarily the OECD guideline?

20 **DR. TIMM:** No, no, we accept the OECD  
21 guideline but when we are, I mean even with the OECD  
22 guideline we could say hey look, you know, do it  
23 according to the OECD guideline but our preference is  
24 to have you do it this way and they may come back and  
25 say hey look, you know, we would prefer to do it this



1 other way and we could get into the discussion and they  
2 may prevail but that's generally the case, if the OECD  
3 guideline allows a wide range of things and we have our  
4 preferences we'll let our preferences be known.

5 **DR. HEERINGA:** Seeing no additional  
6 questions at this point, we'll have a chance to return.  
7 I think we're going to hear public comment, we'll have  
8 a chance to interact there, and before we move on to  
9 the charge questions we'll certainly let Gary Timm and  
10 Dr. Touart open it up for a few additional  
11 clarifications if things have come up, but at this  
12 point I'd like to thank you very much for the  
13 presentations this morning. As I mentioned before the  
14 break, I think the materials were very well organized,  
15 very efficiently presented, I think that's helped  
16 considerably so at this point in time, I think I would  
17 like to move to the period of public comment and for  
18 the audience my aim would be that we will run, since we  
19 started at nine we'll run 'til about 12:30 and then  
20 take a break for lunch at 12:30.

21 Public commenters, a number of people  
22 have registered prior to the meeting, with Jim Downing  
23 the designated Federal official and have been given ten  
24 minutes or extended periods for further presentation,  
25 and I would like to make sure that they hold to that as

1 closely as possible and I'd also like to mention as I  
2 did this morning that if there's anyone else in the  
3 audience who has not registered for a public comment,  
4 but would like to make a public comment, please see him  
5 during the noon hour and I think you'll find the agenda  
6 here for you to make a short public comment.

7 At this point in time I'd like to invite  
8 up our first public commenter and that's Dr.  
9 Christopher Borgert who is with Applied Pharmacology  
10 and Toxicology, Incorporated. Dr. Borgert.

11 There's a public commenter Mike unless  
12 you have a presentation, either one would be fine.  
13 That's great.

14 **DR. BORGERT:** While she's getting that  
15 up I'll first of all, thank you for taking these public  
16 comments and mention that I worked with the American  
17 Chemistry Council in the past on issues related to the  
18 endocrine screening program. My comments are however  
19 my own, I tend to stray far from the farm and won't  
20 hesitate to do that at this juncture.

21 Thank you very much. Okay, we've got  
22 it. I was a member of the EDSTAC Plenary Committee  
23 Screening and Testing Work Group as well. My  
24 perspectives differ a little bit, I was always one of  
25 the folks who was advocating a more streamlined

1 approach in trying to do something, one thing perhaps  
2 well before we got so ambitious to develop a program  
3 that was maybe unwieldy. I want to point out that FQPA  
4 mandated screening and those are supposed to be cost  
5 effective but we really can't evaluate cost  
6 effectiveness unless we know the public health or  
7 environmental problem that the program is supposed to  
8 address so I hope the Agency will define that health  
9 problem so that we can measure it and then measure the  
10 cost effectiveness of this program once it's underway.  
11 Currently the predictive power of the battery and the  
12 assays themselves can only be evaluated in the context  
13 of known positives or negatives.

14 I'm going to talk about the in vitro  
15 assays specifically, these are generally faster and  
16 cheaper, usually considered better suited for  
17 screening, but at this point I would say that none of  
18 the proposed in vitro screens are really fully  
19 validated and standardized and so they're not really  
20 ready. We need better in vitro methods or at least to  
21 shore up the ones we have to best fulfill the goals of  
22 replacing and reducing and refining whole animal  
23 studies so let's get into the assays themselves, I'm  
24 just going to hit a few high points, the estrogen  
25 receptor binding assay or the estrogen receptor

1 transcriptional activation assay probably only assays  
2 that could actually be said to fulfill the mandate to  
3 test for estrogenic activity in humans, I don't think  
4 the program can really go forward without one of them,  
5 but they are not fully validated and standardized so  
6 far. For instance there's still questions about which  
7 cell line or rat size cell should be used, there's  
8 questions about how chemicals that would denature  
9 proteins would behave in this assay, we're going to use  
10 a radial label requiring method or non radial label  
11 that will cut costs and disposal, this assay of course  
12 doesn't differentiate agonists from antagonists and  
13 their other limitations that we know about but there  
14 are some aspects of validation and standardization yet  
15 to complete and I think those are essential. We could  
16 replace that perhaps with the transcription activation  
17 assay which will differentiate agonists from  
18 antagonists, would satisfy the three r's if done in a  
19 helo immortalized human cell line but we have got some  
20 problems, if you peel back the onion skin and look at  
21 the validation data that we wonder what is a positive  
22 response. For instance, the positive control ten  
23 percent gave a thirty percent false positive rate in  
24 this assay so I think some better criteria need to be  
25 established for an acceptable PCX value whatever that X



1 is. Again, cytotoxicity and protein denaturation need  
2 to be, we need to decide how to evaluate those based on  
3 the siferase assay and it's really open to some  
4 confounding so that would need to be worked on and many  
5 of these in vitro assays we talk about the limit dose  
6 being used but nonetheless if you're going to really  
7 interpret the response some other doses are useful and  
8 important but how will that be evaluated in such an  
9 assay, will it be expert judgment, I would favor  
10 certainly stricter statistical criteria. The  
11 validation, OECD's validation was done in Japan, it was  
12 a few labs, just a few chemicals, and much larger scope  
13 is needed so it wouldn't be recommended at this time as  
14 opposed to the binding assay which I think I would  
15 recommend if the validation can be completed.

16           The androgen receptor binding assay is  
17 probably the closest to being validated and  
18 standardized. It does minimize animal use but it does  
19 use animals. Minimizes the use because you can prepare  
20 a back cytosolic fraction but there's the biggest  
21 problem with that assay is you've got to resolve the  
22 issues of preparation of that rat cytosolic fraction.  
23 In the validation efforts some labs obtained fairly  
24 poor results when they used their own preparations.

25           They did much better when the

1 standardized cytosolic preparation was passed around  
2 the labs. This assay is sensitive for chemicals that  
3 bind strongly but less so for weak binders, again I  
4 won't go through all the other limitations, they're in  
5 my more detailed written comments on the slide but this  
6 would be my recommendation but again the validation  
7 needs to have the i's dotted and the t's crossed here,  
8 although this one is the closest.

9           The aromatase assay has some advantages,  
10 it's full in vitro method but again the standardization  
11 and validation are incomplete. There are only a few  
12 laboratories and a few chemicals evaluated while only  
13 one mode of action is evaluated. The assay functions  
14 only on inhibition, misses potential enzyme induction,  
15 again protein denaturation could give false positive  
16 results and other limitations so that would not be a  
17 recommendation of mine at this time. Finally the  
18 steroidogenesis assay again would satisfy the three r's  
19 because of a human 295R cell line standardization and  
20 validation again are incomplete and there are serious  
21 questions about transferability. CSV decided what  
22 culture median, what source of charcoal strip fetal  
23 bovine serum, other things you can read in my bullet  
24 point there, passage number, edge effects, et cetera.  
25 It's still unclear exactly which endpoints would be

1 included and what the performance standards are for  
2 those but those are sorely needed and also how  
3 cytotoxicity will be evaluated. The live dead method  
4 that's recommended by the Agency is somewhat  
5 questionable, the MTT method would be my preference.  
6 It's based on myochondrial function, gives a little  
7 more precursor idea of cytotoxicity than just live dead  
8 cells but it hasn't neither one of those has been  
9 adequately demonstrated. Again some of the same  
10 problems with the other in vitro assays that we know  
11 about but this a too premature stage of validation and  
12 standardization to be recommended at this time so I've  
13 been fairly quick in my comments, to move along and  
14 allow time for other speakers butt I think that these  
15 in vitro assays are key to the screening program and we  
16 really need to do a thorough job of validation  
17 standardization and seriously address at some point  
18 this question of what public health problem is this  
19 meant to remedy. That ultimately should be the  
20 performance standard. Thanks for your attention.

21 **DR. HEERINGA:** Thank you, Dr. Borgert.  
22 Just a second, any questions for Dr. Borgert based on  
23 his presentation? I would like to thank you very much.  
24 At this point I want to move to Dr. Sue Mardy of Dowell  
25 Chemical. Dr. Owens and Dr. O'Connor, I think we'll



1 try to load your presentations over the lunch hour,  
2 just to keep things flowing.

3 **DR. MARDY:** I too would like to thank  
4 the panel for the opportunity to present public  
5 comments. My name is Sue Mardy, and I'm a toxicologist  
6 with Dowell and I have been fortunate at Dowell to get  
7 first hand experience with a number of the Tier 1  
8 assays and I'd like to share some comments on the male  
9 and female pubertal assays today.

10 Just to remind everyone that the  
11 pubertal assay designs, what these are, they start with  
12 weaning rats, females are exposed from day twenty two  
13 to day forty two by oral gavage, we also expose from  
14 day twenty three to fifty three also by oral gavage to  
15 look for changes in the age at puberty onset, vaginal  
16 opening in the females, prepubertal separation in the  
17 males. When vaginal opening has occurred with females  
18 you monitor estrocycline and then at necropsy what  
19 you're looking at is organ weights, you collect blood  
20 for serum hormone measurements and you do histology on  
21 selected organs. More specifically the assay end  
22 points you have two dose levels, one of which is an NTD  
23 which is designed to produce up to a ten percent change  
24 in term of body weights, age evaluated pre pubian  
25 onset, age at first estrous and regularity of estrous

1 cycles in the females and then at necropsy you're  
2 looking at pituitary, adrenal, and thyroid weights in  
3 both males and females, ovarian and uterine weight in  
4 females, testes, epididymis, ventral prostate,  
5 dorsilateral prostate, seminal vesicles, and other  
6 anion weights in the males. Certain hormones that are  
7 measured are T4 and TSH in both genders and  
8 testosterone in the males and then histopathology in  
9 the thyroid, ovaries, uterus, testis and epididymis.

10 Now what I wanted to address today were  
11 some issues in the pubertal assays with respect to  
12 assay specificity. To start with the specificity for  
13 detecting estrogen, androgen, and thyroid active  
14 agents, the assays require a number of apical end  
15 points which can be altered by both endocrine and non  
16 endocrine or systemic toxicity effects. There is an  
17 inherent variability in the age of puberty onset so the  
18 mean age of vaginal opening in the integrated summary  
19 reports varied over a three and a half day range. The  
20 mean age of puberty, preputial separation varied over a  
21 four day range and quite honestly this inter animal  
22 variability of puberty onset is really quite poorly  
23 understood. We do know that puberty onset can be  
24 altered by a number of factors other than just  
25 estrogen, androgen, and thyroid and I've listed a

1 number of those variables on this slide. Estrous  
2 cycles themselves are variable particularly at the  
3 initiation of the estrous cycle and this was shown in  
4 the multi chemical study, multi chemical study that was  
5 done in the integrated summary report where this had  
6 only two of fourteen females that showed estrous  
7 cycling, regular estrous cycling in the control group  
8 so it can be inherently variable just in the initiation  
9 of cycling. Target organ weights can be affected not  
10 only by endocrine active agents but also by stage of  
11 estrous cycle at the time of necropsy and changes in  
12 terminal body weight, so it may be difficult to  
13 determine when you see a positive in this assay whether  
14 or not you have estrogen, androgen, or thyroid active  
15 agents.

16                   Specificity, we've talked a little bit  
17 already about the negative control chemical that was  
18 used in the pubertal assays which was 2-chloromethyl  
19 benzene. This agent affected both males and females in  
20 the pubertal onset assay. Delayed vaginal opening in  
21 the females as well altered a number of thyroid  
22 endpoints. In the males it delayed preputial  
23 separation, affected androgen dependent organ weights  
24 and testis histopathology, Now it's possible that this  
25 was simply a poor choice for a negative compound but it

1 still leaves the author the question as to whether or  
2 not this assay is prone to non specific effects  
3 resulting in a high frequency of false positives. In  
4 the assay recommendation paper that recently was  
5 released, it said although a toxic negative chemical  
6 has not been identified, several chemicals positive for  
7 one of the mode of acts...one of the modes of action  
8 have been found to be negative for other modes of  
9 action evaluated in this assay, and this concept is  
10 difficult to apply consistently across the data set of  
11 data in the integrated summary reports for the pubertal  
12 assays. For example, if you consider phenobarbital  
13 which was used as a positive thyroid agent in a number  
14 of Tier 1 assays, phenobarbital was detected in the  
15 male pubertal assays for effects on reproductive end  
16 points not effects on thyroid so obviously this case  
17 you wouldn't report that phenobarbital would be a  
18 negative control for thyroid end points in this assay.  
19 That's a difficult concept to uphold across the data  
20 set and in addition it still doesn't answer the  
21 question as to whether or not systemic toxicity by non  
22 endocrine active chemicals might produce positive assay  
23 results.

24 The maximum tolerated dose that's been  
25 proposed for the pubertal assay is a dose level that

1 would be considered to be at or just below the maximum  
2 tolerated dose would be a dose that caused the body  
3 weight changes of no greater than approximately ten  
4 percent of the mean for the controls. We believe that  
5 body weight decreases that are approach or equal ten  
6 percent are not appropriate for the pubertal assay  
7 maximum tolerated dose. These are effects of body  
8 weight on the organ weight end points to the female  
9 pubertal assay. This was a feed restriction study that  
10 was done by Susan Laws at the EPA. For this study  
11 again it was feed restriction using the female pubertal  
12 assay design. There were no chemical treatments and  
13 what I did was under the terminal body weight column  
14 you can see changes in terminal body weight with  
15 increasing magnitude of change. Two percent, five  
16 percent, twelve percent, twenty percent, and what you  
17 can see is that a twelve percent change in terminal  
18 body weight affected pituitary weights, adrenal  
19 weights, and ovary weights. On the maximum tolerated  
20 doses designed to be less than equal to ten percent.  
21 We don't know exactly what they'll do to assay end  
22 points, but we do know that somewhere in between five  
23 and twelve percent there's a significant change in the  
24 number of organ weights that we measure.

25 This is the body weight effects on the

1 male pubertal assay and this there are more feed  
2 restriction studies from which to draw so I've listed  
3 those in the left hand column. Terminal body weight  
4 changes, you can see there about the fourth column from  
5 the left and I've put them in ascending order for the  
6 magnitude change in body weight. Again no chemical  
7 treatment, just feed restriction through the pubertal  
8 assay design and what you can see is that at a four  
9 percent change in body weight there was already a  
10 significant change in pituitary weights, up an eleven  
11 percent change in body weight there was a significant  
12 change in epididymal weights, ventral prostate weights,  
13 seminal vesicle weights and dorsilateral prostate  
14 weights which I didn't list up there. So you can see  
15 somewhere again in between where we see a four and  
16 eleven percent change in body weight we have a number  
17 of significant changes in organ weight end points. I  
18 should also mention as well that there are a number of  
19 assay end points from the pubertal assays which hadn't  
20 been looked at for whether or not body weight effects  
21 might impact them from, for instance level A9 which has  
22 never been addressed with respect to body weight  
23 changes nor have initiation of regular estrous cycles  
24 been looked at.

25 On statistical analysis the integrated

1 summary reports state that body weight mediated  
2 differences in organ weights can be alleviated by  
3 evaluating organ weights on a relative weight basis.  
4 However this analysis is not permitted according to the  
5 pubertal assay designs. What's recommended is a  
6 covariant analysis, covarying with body weight at  
7 weaning. Now this isn't appropriate with respect to  
8 statistical practices in that you have a covariant that  
9 is not affected by treatment. However, we know that  
10 body weight affects a number of these end points and it  
11 doesn't account for body weight effects, terminal body  
12 weight effects on organ weights. There has been a  
13 recommendation in the past that covariant analysis can  
14 be done with terminal body weights, Muscale and Torry  
15 have made that kind of recommendation. I myself am not  
16 a statistician but I would implore this group to  
17 consider whether or not there might not be an  
18 alternative statistical approach.

19               So in closing I just want to say that  
20 the end points, a number of the end points in the male,  
21 female pubertal assays are apical and do have some  
22 inherent variability, so it may be difficult to  
23 determine whether chemicals have estrogen, androgen or  
24 thyroid effects. The assays have not been adequately  
25 validated for specificity, there's no evidence that the



1 assays are specific for just endocrine acting  
2 materials. We have no negative control data using a  
3 negative control chemical. Ten percent change in  
4 terminal body weight is likely to alter assay end  
5 points, we've seen this with feed restriction data and  
6 we don't feel that those statistics that are  
7 recommended for the assays are going to adequately  
8 consider changes in terminal body weight with respect  
9 to these organ weights.

10 We'd like that the MPD be reconsidered  
11 for these assays. The problem with this is that the  
12 assays may produce a high rate of false positives which  
13 is my final slide, so it's the impact of false  
14 positives with the pubertal assays. Well, the pubertal  
15 assays are designed to detect modes of action that are  
16 not readily detected by a number of assays. Because  
17 they're in vivo they can detect activity of metabolites  
18 that you won't see in in vitro assays. Positive  
19 results for pubertal assays may be difficult to refute  
20 and could trigger Tier 2 testing. Tier 2 testing is  
21 going to be costly, resource intensive, and is going to  
22 use large numbers of animals. Multi generation study  
23 costs half a million dollars on average and uses more  
24 than twenty seven hundred rats. Compare this with the  
25 other Tier 2 tests which include studies on fish,

1 birds, and amphibians, and that's going to be a lot of  
2 animals that are going to be used. And costs will  
3 easily exceed a million dollars per chemical. We also  
4 face product deselection in between generated Tier 1  
5 results and being able to follow through with full Tier  
6 2 testing. Thank you.

7 **DR. HEERINGA:** Thank you, Dr. Mardy. I  
8 would ask the panel at this point. Are there are any  
9 questions? Dr. Chambers?

10 **DR. CHAMBERS:** Dr. Mardy, one of your  
11 earlier slides said there was some variability in the  
12 days required for vaginal opening, preputial separation  
13 I think, is that what you said? Were you meaning  
14 between different laboratories or among the same  
15 animals in the same laboratory test?

16 **DR. MARDY:** You can see within the  
17 same...that happens to be, that study data that I  
18 showed you is across laboratories but within the same  
19 laboratory from time to time, you can see that  
20 variability and there's a very nice data set that was  
21 published by Merck which included thirty five studies  
22 in which they looked at puberty onset and it showed  
23 exactly the same span for males and females so even  
24 within the same lab.

25 **DR. HEERINGA:** Thank you very much, Dr.

1 Mardy. At this point in time I would like to do a  
2 little check here. I tell you what, rather than  
3 getting too far out of order with the agenda, we are at  
4 12:00 and we have a number of public commenters I  
5 think, several, who need to load their presentations so  
6 what I'd like to do is call a lunch hour at this point  
7 and ask that we...let's reconvene at 1:15, that gives  
8 everybody a little over an hour for lunch and at that  
9 point in time we will continue with the public  
10 comments.

11 What I would ask though is that anyone  
12 who does have a presentation is scheduled for public  
13 comment this afternoon that you coordinate with Dr.  
14 Madden to make sure that your presentation is loaded on  
15 the presentation lap top so thank you, everybody and  
16 we'll see you at, what did I say, quarter after, well,  
17 1:15.

18 (WHEREUPON, recess was taken for lunch.)

19 DR. HEERINGA: We'll get back underway,  
20 please. Welcome back everyone to the afternoon  
21 session, our first day meeting of the FIFRA Science  
22 Advisory Panel on the topic of the Endocrine Disruptor  
23 Screening Program Proposed Tier-1 Screening Battery.  
24 At this point in time we are in the process of the  
25 period of public comment, and we have heard prior to

1 the lunch hour from Dr. Chris Borgert and Dr. Sue  
2 Mardy. And I believe at this point we are up to Dr.  
3 Owens who is here from Procter and Gamble.

4 **DR. OWENS:** Let me see if this works.  
5 Okay. Somebody needs to underline this, pretty please.  
6 Just to -- I'll start off with the first slide which  
7 did say Willie Owens of Procter and Gamble Central  
8 Product Safety. There's also in a sense some  
9 transparent disclosures, and that is I've worked with  
10 the OECD since 1999 as an industry member of their  
11 validation management group, and that is for the  
12 Hershberger, the uterotrophic, et cetera. Did not  
13 conduct any of the laboratory work but was heavily  
14 involved in writing the reports, the peer review for  
15 the uterotrophic. I actually was seconded to the OECD  
16 and had a pleasant stay in Paris for a year. I have  
17 also here in the US been a member of the FACA, et  
18 cetera. So I'm interwoven with a number of the assays  
19 et cetera, particularly the uterotrophic and the  
20 Hershberger that I will speak about we hope.

21 **DR. HEERINGA:** We'll take a moment until  
22 Charlene gets that brought up.

23 **DR. OWENS:** Certainly. Just trying to  
24 make the best use of time here.

25 **DR. HEERINGA:** There we go.

1 **DR. OWENS:** All right. Now that we've  
2 done the formalities. We'll move down. The basic  
3 views here for this presentation is not one of  
4 complaint. It's one of good news. It's both of the  
5 assays, the uterotrophic and the Hershberger have been  
6 through an international validation program. They are  
7 found to be satisfactory. They have complied with all  
8 of the criteria in the OECD Guidance Document 34, which  
9 addresses validation, et cetera. So I'll be giving you  
10 some background. I think there's also some learning  
11 points in some of the questions and comments I heard  
12 this morning.

13 Basically the rationale for the assays  
14 is extremely straightforward. The estrogens and the  
15 androgens, of course, and actually regulates specific  
16 male and female target tissues. Fortunately, in most  
17 cases this growth is specific. It's rapid. There is a  
18 significant percent change or magnitude of response,  
19 and particularly with the male tissues, if your  
20 dissection is good, you can keep control of the  
21 coefficients of variation. So quite frankly, you can,  
22 with a den of only six animals per group, get very good  
23 results. Also the assays were developed actually in  
24 the 30s. The original Hershberger itself was without  
25 the muscle complex. It's been refined in the

1 pharmaceutical industry. It's also been adapted to  
2 antagonist in both cases. It's also been adapted in  
3 both cases to specific inhibitors, that is for  
4 aromatase. You take the immature animal with the  
5 ovaries still present. You coadminister an  
6 aromatizable androgen and with a given inhibitor, and  
7 you can get a nice dose response based upon uterine  
8 weight. Also there were public health studies for both  
9 of these assays in the 60s, massive inter-laboratory  
10 study, over 700 compounds for each assay, the problem  
11 being that most of these were steroidal compounds.  
12 They weren't commercial compounds.

13           Now quickly, the program with the OECD,  
14 there were videos and dissection guides, figures, et  
15 cetera. Roll over here to the dissection guide for the  
16 Hershberger. The test protocol was sent out to a  
17 number of laboratories in international settings,  
18 primarily because English as a second language issue.  
19 The statistical powwow was analyzed thanks to Joe  
20 Haissman, and then the protocols were normally tested  
21 in a phase 1 with open compounds. From there a dose  
22 response with weak positive commercial compounds was  
23 carried out in phase 2. Then in phase 3, there were  
24 coated substances. Since working with coated  
25 substances to avoid bias and subjectivity in the

laboratories, there's a criteria under Guidance Document 34 which should be applied flexibly. Negatives and the same dose for all of the weak positives in phase 2 were used in phase 3 basically so could address the other criteria - are the laboratories as a whole getting the same result over time.

Now in the utero-trophic, and we've got an exhibit, the issue that has come up again and again of dietary phytoestrogens was addressed.

Briefly the overview of the utero-trophic. There are a number of elements that were standardized in the left column, and recalling this was intended as an international test guideline and also as a screen. There were a number of parameters that were allowed to vary, but for example, both Wistars and SD's, Sprague Dawleys were in the validation program. And these were also co-analyzed.

Now top line on the left is the epi needle estradiol and to assure indeed we were working with a set of weak compounds, you can see where they sit on the overall dose response curve. The VPA, and that was the OP prime of DDT. Going on, you'll see here a comment from this morning. You can see the immature gavage and SC the adult ovex SC at three and seven days. There was a great deal, shall we say, of



1 controversy about whether the ovex was indeed superior  
2 or not. The bottom line is it's equivalent. The power  
3 differences come down to the third decimal place; so  
4 they are basically equivalent. You'll also see gavage  
5 in SC were run, and there quite frankly the DDT and the  
6 methoxychlor were more potent if administered orally.  
7 The others if SC. The guideline in reference to the  
8 comments that Gary made this morning, the guideline  
9 basically indicates in guidance that you should use the  
10 relevant route of exposure. Now personally and in  
11 context of my employer for animal welfare, frankly  
12 choosing a default SC is a misuse of animals. It's not  
13 ethical. Use the relevant route of exposure of the  
14 dose is straightforward. So I would urge you to think  
15 about that point quite carefully.

16           The Hershberger linger on -- you'll see  
17 the dose up at the top of the slide -- is the weaker  
18 antiandrogen in a number of the assays. What you have  
19 here is the dose from phase 2 in four labs on the X-  
20 axis and the coated same dose from 10 laboratories in  
21 phase 3 on the Y-axis. What I've done is here are the  
22 means, across, and we've plotted them. So the body  
23 weight decreases slightly. Then there's the glans  
24 penis. Cows is Cowper's glands, the muscle complex,  
25 ventral prostrate, and seminal vesicles coagulating

1 gland. Okay. That approximates the response of each  
2 of these tissues with the other antiandrogens in terms  
3 of a decrease. And I admit, like you, I was quite  
4 surprised by the R-square.

5 Now one of the elements that, quite  
6 frankly, was mentioned this morning is what about in-  
7 utero exposures. In validations programs are what's  
8 called, rightly or wrongly, a predication model. It's  
9 really a correlation or correspondence test. How well  
10 does the screen do against higher tier assays? What  
11 you have here are the five weak positives, and there in  
12 the central column is the utero-trophic minimal  
13 effective dose by oral gavage. And over on the right-  
14 hand column you have, either from a pubertal type  
15 assay, an in-utero type assay, or a full multi-gen de-  
16 correspondence of the doses. You will see that for  
17 this phenol-A at the bottom there is not. Remember  
18 we're working with three administrations with necropsy  
19 on the fourth day; other toxicities, quite frankly,  
20 don't come through. And so you can actually press  
21 these animals well above the, what I call a normal MTD,  
22 and in this case the so-called estrogenicity doesn't  
23 come through in the multi-gen.

24 Now I'll put this down. Now importantly  
25 here on the Hershberger, here the in-utero effects are

1 drastic and irreversible for antiandrogens, and it  
2 deserves close examination. You can see its minimal  
3 effective dose and, quite frankly, relatively sensitive  
4 endpoints in terms of anogenital distance, and retained  
5 nipples in the male animals, and where you've had in-  
6 utero exposure in the proper window in the dams. The  
7 net result is, quite frankly, compare the screening  
8 data, compare the higher tier data. And I think in a  
9 question that was asked this morning is you can see if  
10 indeed there is a lack of sensitivity in the screen or  
11 there is a good correspondence in the screen? And  
12 that's why the criteria to make this comparison is part  
13 of a validation program for Guidance Document 34. It  
14 is, I will point out, something absent in many of the  
15 other assays. But I think you can see its power and  
16 its utility.

17 Now the phytoestrogens to try and  
18 explain the slides and the procedures is here are the  
19 data for non-phenol in the intact in the tiers. It's a  
20 relatively high dose of 250. That will exceed the MTD  
21 in longer assays. The diamonds are the means. Those  
22 bars are not SDs or SEs. They are actually the upper  
23 and lower 95% confidence levels. Remember you've got  
24 an NO6, and if the lower part of the bar exceeds a  
25 value of 1, indeed you are statistically significant.

1 These are from dietary assays on the phytoestrogens.

2 Here you'll see that, one, the means do not decline  
3 despite as phytoestrogen levels increase. Neither is  
4 there an absence of sensitivity as the phytoestrogen  
5 levels increase.

6 In another set over on the far right at  
7 about 85, there was one laboratory that did with other  
8 issues. So an apparent decrease in a test guidelines.  
9 Therefore, there is a ceiling on the phytoestrogens in  
10 the uterotrophic assay in order not to lose any  
11 sensitivity in the assay, but, again, the issue has  
12 been addressed.

13 Again, as I begin to close down here,  
14 these on the table are the various criteria in Guidance  
15 Document 34, paraphrased mind you. Both the utero and  
16 the Hershberger have complied with all of them. I  
17 would urge you to go forward and ensure that other  
18 tables are self-instructed, so you know if the assays  
19 presented to you are in full compliance and what is the  
20 rationale if something is lacking. Finally conclusion,  
21 the EDSTAC battery quite frankly is seriously outdated.  
22 It was conceived in 1996. The uterotrophic and  
23 Hershberger are fully validated. They're accepted for  
24 EA and Anti-A. They are also even now in use by  
25 Europe, Japan, and others. There is also a significant

1 data set approaching a 1000 compounds for the  
2 uterotrophic in Japan. I can also assure you that  
3 industry in Europe has also run a number of compounds  
4 according to these guidelines. It would be  
5 inappropriate to repeat data. So how to use and  
6 acquire these data is one of the things that confronts  
7 you to minimize animal use. On the thyroid, there is  
8 also 28 and 90-day repeat dose. We also have the reach  
9 legislation in Europe where many of the assays, higher  
10 tier assays, are going to be de facto. And do you use  
11 the data available to see if you need to screen. Then  
12 finally highly specific, small-M, in-vitro can proceed.  
13 How do you arrange a battery that is fully compatible  
14 with the RRR's in terms of animal use? And finally I  
15 would argue that complex animal-intensive assays such  
16 as the pubertal shouldn't be used in a default routine  
17 requirement pending other available information. In  
18 other words, the battery itself should not be a default  
19 checklist but appropriate to the information that's  
20 available, both at higher tier and existing tiers,  
21 lower tiers, for a compound. Thank you. And in  
22 interest of time, any questions?

23 **DR. HEERINGA:** Any questions for Dr.  
24 Owens? Yes, Dr. Eldridge.

25 **DR. ELDRIDGE:** Uh, Chuck Eldridge, Lake

1 Forest. Um, Dr. Owens, what would be your opinion of  
2 using the uterotrophic assay to identify estrogen  
3 antagonism as well as agonist.

4 **DR. OWENS:** In the case of the  
5 antagonist, the OECD has written a guideline. You will  
6 note that I had up there E-A and Anti-A. The peer  
7 review noted that only a single potent antiestrogen had  
8 been used. The data was reproducible across labs. No  
9 evidence of CD problems, but, quite frankly, were  
10 absent a battery of weak antiestrogen commercial  
11 chemicals to take the assay forward in terms of a true  
12 validation program. There is nothing on paper that  
13 would say it cannot be used, and, in fact, in the  
14 phase-1 report if you want to refer to it, all of the  
15 data is there on the antiestrogen phase-1, again, a  
16 single potent compound for a shakedown of the protocol.  
17 Protocol was adequate. So in terms of you have a green  
18 light to proceed, but the question is, is do you have  
19 actual data in hand established to say that it is valid  
20 for that use. Therefore, it is not in the test  
21 guideline. It is only in an associated guidance  
22 document with the OECD. There are no technical  
23 barriers. There is the regulatory requirement for  
24 validation that would be the hurdle. Let me add  
25 though, that confronts any of the other assays also is

1 there are a very limited number of antiestrogens, so  
2 all of the other assays are in the same boat.

3 **DR. ELDRIDGE:** Thank you very much.

4 **DR. HEERINGA:** Thank you very much,  
5 Dr. Owens. At this point in time I would like to  
6 invite up Dr. John O'Connor, who is with Dupont Haskell  
7 Global Centers for Health and Environmental Sciences.

8 Dr. O'Connor?

9 **DR. BECKER:** Mr. Chairman, it's Rick  
10 Becker with ACC. If we could just switch, that might  
11 be better.

12 **DR. HEERINGA:** Sure.

13 **DR. BECKER:** Thank you.

14 **DR. HEERINGA:** No problem.

15 **DR. BECKER:** But now we close --

16 **DR. HEERINGA:** Yeah. Close the computer.

17 **DR. BECKER:** Sorry.

18 **DR. HEERINGA:** Why don't you leave the  
19 computer open, I think.

20 **DR. BECKER:** Well that was good. Thank  
21 you, Mr. Chairman. Thank you, again, to the EPA for  
22 this meeting, and thank you for allowing us to provide  
23 our comments at this time. This is a critically  
24 important issue obviously from a chemicals industry  
25 perspective. Just to note that we supplied written



1 comments late last week and appreciate the, you know,  
2 this was up against the deadline. I wanted to thank  
3 the EPA for receiving those comments and sending those  
4 out quickly so that the Science Advisory Panel members  
5 had a chance to have those before the meeting. I  
6 particularly appreciate that. So as we go through some  
7 of these slides, if there's additional information that  
8 we just cover very quickly, I would refer you to those  
9 written comments.

10 I want to talk to day briefly about the  
11 15-day intact male, adult male assay for the Endocrine  
12 Disruptive Tier-1 Screening Battery. I'm a  
13 toxicologist with the American Chemistry Counsel, a  
14 trade association that represents the commodity  
15 chemical manufacturers in the United States. I've been  
16 working with that organization for almost, more than  
17 nine years now, and have been engaged with the  
18 endocrine program since the time that I joined.

19 You've seen a slide like this similarly  
20 in the presentation from the EPA staff, so I won't go  
21 into great detail on this. But just to note that the  
22 EDSTAC recommendations here did include, in fact, I'll  
23 turn to screening battery number one, an alternate to  
24 the recommended screening battery, and that alternate  
25 included the adult male assay. And then there was also

1 an alternate too that was discussed earlier. Well as  
2 folks have indicated, since that time a significant  
3 amount of laboratory has gone on to develop the  
4 methods, to evaluate them, to standardize them, and to  
5 validate them. And so things have changed as to be  
6 expected in a scientific endeavor like this. So where  
7 are we at today? Well in March, just recently in this  
8 year, the EPA has proposed this new screening battery,  
9 which differs, as was pointed out, significantly from  
10 the EDSTAC recommended battery. On the left-hand-side  
11 I've listed the EPA's newly proposed screening battery.  
12 The ones in red there are the assays that I  
13 particularly want to talk about, the contrast or  
14 compare to the intact adult male rate assay. And so  
15 what we want to talk about today, what I'd like to at  
16 least introduce today is a recommendation to streamline  
17 and appropriately focus the tier-1 screening battery,  
18 which would substitute the intact adult male assay for  
19 those outlined in red on the left-hand-side. For the  
20 steroidogenesis assay in lieu of the pubertal female  
21 assay, in lieu of the pubertal male assay, and in lieu  
22 of the amphibian metamorphosis assay.

23 I think ever speak has talked about the  
24 societal attributes. So I won't go into great detail  
25 other than to say that the fact is that if these assays

1 can be sensitive and specific at the same time, that's  
2 the most desirable attribute that we can have, as well  
3 as cost effective and quick. So I think there is this  
4 issue about low-false negatives, but we also want to  
5 make sure there is an acceptable degree of false  
6 positives. If that sieve is too wide and everything  
7 comes through as a positive, it really doesn't help  
8 distinguish the true substances that you need to go on  
9 and focus on versus those that are of lower priority.  
10 So the study design of the intact adult male rat assay  
11 is depicted here; young adult animals, 10-week old, 15  
12 per group, three dose groups plus a control, and the  
13 test substance is administered orally for 15 days. The  
14 endpoints to focus on here are, to point out, is the  
15 hormonal battery, a comprehensive hormonal battery,  
16 serum hormones, testosterone, THT, estradiol, prolactin  
17 LH, FSH, T3, T4, and TSH coupled with organ weight and  
18 focused histopathology, testis, epididymis and thyroid.  
19 And, if necessary, biochemical preparation of the  
20 padded microsome for later evaluation, if needed. Of  
21 course you're working with the intact animals, so you  
22 have the intact hypothalamic pituitary testis axis.  
23 You've seen similar slides like this, so the X  
24 indicates those areas in which interactions can be  
25 detected and measured in this assay.

1 One of the real advantages of this assay  
2 is it is a mode of action screening assay. It focuses  
3 on mechanistic endpoints, non-apical endpoints, and so  
4 the advantage with this is that you can get a profile  
5 of responses that would be predictive of a particular  
6 mode or mechanism of action. So just as shown here, if  
7 you've looked at the substance, it would be an estrogen  
8 receptor agonist. The ASG would either be not changed  
9 or decreased, no effect on thyroid, decrease in  
10 testosterone, no effect or decrease in E2, prolactin  
11 increased, LH and FSH plus or minus, and then TSH and  
12 T4 no change. And so you can use this profile then to  
13 help you identify what particular mode of action of  
14 your unknown substance is, and this will be very  
15 helpful, I think, in trying to further understand and  
16 interpret the tier-1 screening battery as you go  
17 forward in trying to integrate the results from the  
18 various screens and tests.

19 The EAC, the endocrine active compounds,  
20 that have been evaluated in this assay during its  
21 develop standardization and validation are listed here.  
22 I won't go through every one of them, but just to point  
23 out that it's a full range of endocrine active  
24 substances. Estrogen agonists, androgen agonists and  
25 anti-agonists, as well as progesterone-receptor

1 agonist, antagonist, dopamine agonist, antagonist,  
2 thyroid hormone agents, steroidal genius inhibitors and  
3 also aromatase substances.

4           We've also evaluated in this assay an  
5 allyl alcohol, which is a negative control chemical.  
6 We heard earlier today some discussion about the  
7 failure of the EPA studies to evaluate or to come up  
8 with a negative control chemical in pubertal assays.  
9 In this came, and similar to what was done earlier in  
10 the other multimodal assays, specificity is usually  
11 evaluated with substances of known mode of action and  
12 then following that particular pathway, in looking at  
13 expected responses and making sure you don't get the  
14 unexpected responses. So you don't get androgen  
15 responses when you're testing an estrogenic agent and  
16 vise versa, but I think it's also important, as Dr.  
17 Marty pointed out, to look at negative control  
18 chemicals, in particular when we're going to be testing  
19 substances with unknown activity in fairly high doses.  
20 It's important to have that degree of specificity, and  
21 so allyl alcohol was one chemical that was tested as a  
22 negative control chemical and shown to be negative in  
23 this assay.

24           We have, in addition, initiated just  
25 this year some ongoing studies to continue with and

1 complete the validation studies of this assay. Two  
2 testing laboratories each will be testing four  
3 substances, allyl alcohol as a negative control, DE71,  
4 iopanoic lactone, and of course allyl alcohol is the  
5 compound that was tested earlier. So when these  
6 studies are completed by the end of this year, then  
7 we'll have a better data set in which to evaluate of  
8 the negative test article, negative androgen control  
9 chemical as well as some thyroid-monitored chemicals  
10 and aromatase inhibitors.

11           So there's some advantages to using the  
12 adult male assay in lieu of the pubertal assays in  
13 tier-1 screening. It's a mode of action screen. It's  
14 comprehension, sensitive, and specific. It's apical of  
15 evaluating many different modes of action in a single  
16 assay, focusing on mechanistic endpoints not apical  
17 endpoints. So it's focused on trying to evaluate EAT  
18 activity specifically. It allows for that profile  
19 interpretation that I mentioned. I think it's  
20 sensitive and specific enough for the purposes of tier-  
21 1. As indicated here, it will reduce the numbers of  
22 animals needed. The pubertal tests require male and  
23 female, two dose levels plus a control, 15 per each,  
24 and this is 15 animals in those groups in a control.  
25 The other thing which was also mentioned this morning

1 is this mode of action assay, as indicated here, you  
2 can add additional endpoints if needed as you go  
3 forward because it is really focused on evaluating the  
4 serum hormones or other hormone activities.

5 So I'll end with that and say thank you  
6 very much. I appreciate it.

7 **DR. HEERINGA:** Are there any questions  
8 for Dr. Becker on his presentation from the panel?  
9 Thank you very much, Dr. Becker. Is Dr. O'Connor a go  
10 at this point? John O'Connor, again, as I mentioned  
11 from the Dupont Haskell Global Centers for Health and  
12 Environmental Sciences. Dr. O'Connor?

13 **DR. O'CONNOR:** Well I thank you very  
14 much. I appreciate the opportunity to talk today in  
15 hear comments. And what I want to do is basically add  
16 to what Dr. Becker has talked about with respect to the  
17 15-day intact adult male rat assay. And I've been at  
18 Dupont for 18 years now and working in the endocrine  
19 screening and working with endocrine disruption issues  
20 relative to Dupont Chemicals for about the past 10 or  
21 12 years. And so a lot of the work that I've done has  
22 actually been related to the pre-validation work for  
23 the intact adult male rat assay.

24 So, again, I don't want to spend any  
25 time on this. I just want to point out that really



1 what I'm going to do is I want to just give you some  
2 examples of some of the aspects of the 15-day intact  
3 adult male rate assay that we feel make it a more  
4 attractive assay to include in a tier-1 screen than the  
5 pubertal assays, and how we perceive this kind of  
6 replacing those two assays. Again the study design as  
7 Dr. Becker has already discussed, and, again, the key  
8 points here are we do have organ waste and  
9 histopathologies similar to what is used in the  
10 pubertal assays. The real difference is that we have  
11 this comprehensive hormonal assessment, and there is  
12 limited hormonal endpoints that are evaluated in this  
13 pubertal animals, specifically for the thyroid. But  
14 the comprehensive hormonal battery here allows us to  
15 really differentiate mode of action, which again can be  
16 valuable for setting up tier-2 tests, and I'll give an  
17 example of that later on.

18 So this table, I apologize for the small  
19 font, but essentially this summarizes the compounds  
20 that have been evaluated in the intact adult male  
21 assay. You can see there are over 25 chemicals. The  
22 testing laboratory is indicated there. On the right  
23 side it basically indicates whether it has been or has  
24 not been detected successfully in the intact adult male  
25 rat assay. You will see there are two piloted and read

1 there are no, and just to point out that both those  
2 chemicals were not run as MTD. So it is unclear if it  
3 would be detected if they ran them up to the MTD. The  
4 other thing to point out again, allyl alcohol, the  
5 negative control chemical that we ran that is a hepatic  
6 toxin. We did detect as a negative chemical in this  
7 assay, and I will show that data in a little bit. The  
8 two chemicals that are highlighted in the gray  
9 represent the two chemicals that were part of the EPA's  
10 sponsored validation effort of the intact adult male  
11 rat assay. So one of the real negatives for this assay  
12 has been that it hasn't gone through the amount of  
13 actual validation work that some of the other assays  
14 have, but there has been, as you can see here, quite a  
15 bit of pre-validation work that has been done.

16               Again, as Dr. Becker indicated, we are  
17 in the process of doing some additional validation  
18 through some ACC sponsored work. EPA has been involved  
19 in discussions around laboratory selection and chemical  
20 selection for these. So, again, we continue to  
21 generate data for validation of this assay we move  
22 forward.

23               Just a comparison to the pubertal  
24 assays. I'm not going to say that this is a 100%  
25 complete list of chemicals that have been run in

1 pubertal assays, but it should represent a majority of  
2 them for sure. Again, what's indicated here in red are  
3 chemicals that were not identified they say to a red  
4 note in those assays. And then, again, I'd like to  
5 point out, as Dr. Marty has pointed out earlier, 2-  
6 chloronitrbenzene at the bottom, which was actually  
7 identified as an endocrine active chemical even though  
8 it was ran as a non-endocrine active control chemical.

9           So one of the big issues with one of  
10 these, with the assays, in particular pubertal assays,  
11 is really trying to define the MTD, and as part of the  
12 pre-validation work, an experiment was run to  
13 essentially look at where body weight effects in the  
14 intact adult male rat assay will cause endocrine-like  
15 effects or cause effects on the endpoints of the intact  
16 male assay. I don't want to go through this in detail,  
17 but as you can see, this line summarizes the organ-like  
18 data and the next two summarize the hormonal endpoint  
19 data. Where if you targeted MTD in the intact adult  
20 male rat assay that was no greater than 10% difference  
21 in final body weight at the end of the 15-day test, you  
22 can see that there are no effects on any of the  
23 endpoints that would be evaluated. And, again, the  
24 next two slides show the serum hormone data, which  
25 should, again, by targeting that 10% difference in

1 final body weight, you don't have any effects due to  
2 secondary body weight.

3           One of the other questions and one of  
4 the other criticisms of the intact adult male rat assay  
5 has been the fact that for the most part its dogma is  
6 that the immature animals are much more sensitive for  
7 detecting endocrine active chemicals than mature  
8 animals, but unfortunately there's not a lot of good  
9 literature out there to really compare that within the  
10 context of one study design. So what we did was ran an  
11 experiment to really compare immature and mature  
12 animals within the context of a single study, in this  
13 case using a 15-day duration by oral route. Again, in  
14 a 15, same exact study designed for the intact adult  
15 male rat assay but with immature animals and mature  
16 animals at the same doses so we can compare the  
17 responses and get an idea of what the sensitivity  
18 differences might be.

19           We tested this with six chemicals as  
20 listed down on the bottom here. I just want to show a  
21 few chemicals. So this is the data for Vinclozolin.  
22 On the left side are the immature animals. On the  
23 right side are the adult animals. The age indicates  
24 that day at which they went to necropsy. Okay. So at  
25 53 days of age is equivalent to what is used for the

1 pubertal male assay. And if you look at the bottom, so  
2 this is looking at epididymis, seminal vesicle and  
3 prostate rate after treatment with Vinclozolin for 15  
4 days. You can see that between the immature and the  
5 mature animals, the responses are really pretty  
6 similar. There is not a whole lot of difference there.

7 If you look at the serum hormone data,  
8 again, you see a similar pattern there in that  
9 biologically the responses, the sensitivity between the  
10 mature and immature animals are pretty similar. Okay.  
11 And then looking at data for phenobarbital, in this  
12 case looking only at the thyroid hormone data, the  
13 thyroid weight was increased in the mature rats but was  
14 not increased in the immature rats. But essentially,  
15 again, what you see is that there aren't a whole lot of  
16 differences between the immature and mature animals.

17 Now, again, I didn't show all the data  
18 for the six chemicals, but what, to summarize all six  
19 chemicals, essentially this is the same pattern that  
20 you see for the immature and the mature animals when  
21 you run them within the context of the single study  
22 design, in this case with necropsy occurring on day 53  
23 days of age for the immature and day 84, 84 days of age  
24 for the mature animals.

25 This data is the data from the allyl

1 alcohol study, and, again, the importance here is that,  
2 you know, as we develop these assays for detecting  
3 endocrine active chemicals, we need to be certain if we  
4 run a negative chemical that is expected to be a non-  
5 endocrine active chemical, that it will, in fact, be  
6 identified as a non-endocrine active chemical. And,  
7 again, if you look here in this study, we did achieve  
8 MTD of 90% final body weight in the high dose level.  
9 There were no effects on organ weights. There was no  
10 effects on histopathology, although that data is not  
11 shown. There were a few effects on the serum hormone  
12 levels, specifically a decrease in testosterone and DHT  
13 at the high dose and has sporadic effects on prolactin  
14 at the 40 mg/kg/day dose. But essentially we consider  
15 this a negative compound based on the fact that we  
16 weigh the organ weight and histopathology data higher  
17 than the hormonal data. So in the case here where we  
18 have just a single statistically significant change at  
19 high dose only, we would not necessarily consider that  
20 a positive response. But, again, keep in mind that  
21 with this assay, as any other assay in any tier-1  
22 screening battery, you are considering the weight of  
23 evidence from all of the assays.

24 And then finally I'd like to end by  
25 going over a brief case study with flutamide,

1 ketoconazole and finasteride. I don't want to show,  
2 I'm not going to show you actual data. This has been  
3 published. In this case we're looking at flutamide,  
4 which is an antiandrogen, finasteride, which is a 5-  
5 alpha-reductase inhibitor, and ketoconazole, which is a  
6 testosterone biosynthesis inhibitor. Well if you look  
7 at the data, and, again, this is just a summary of the  
8 data, but if you look at the organ weight data alone,  
9 and, again, this is similar to what would be done in  
10 the pubertal assay, you can see that all three of these  
11 test substances decrease the androgen-independent  
12 tissue weights. So if you're looking only at organ  
13 weights, you cannot differentiate mode of action.  
14 However, if you couple that with the serum hormone  
15 data, in this case looking at testosterone DHT, FSH,  
16 and LH, you can actually determine the mode of action  
17 by the hormonal pattern. And, again, I'm not going to  
18 go into looking at this, but suffice it to say that if  
19 you sit down and think about the biology, the responses  
20 do make sense and are consistent with the specific  
21 modes of action for flutamide, ketoconazole, and  
22 finasteride. So, again, this is the value of a mode of  
23 action screening battery. It can allow us to tailor  
24 those tier-2 tests to more effectively identify those  
25 endocrine active chemicals.



1 So for data interpretation, again, the  
2 key here is that the high dose level should not exceed  
3 an MTD, and for the adult animals it's fairly easy to  
4 define that MTD, again, in contrast to the pubertal  
5 animals where it's much more different. The organ  
6 weight and histopathology data is weighted more than  
7 the hormonal data, again, because the hormonal data is  
8 inherently more variable. But, again, when you're  
9 looking at the data from any tier-1 screen assay, you  
10 need to consider the weight of evidence from all of the  
11 tests in that screening battery itself.

12 And then finally, this the proposed  
13 tier-1 screening battery again that we're recommending,  
14 which in this case we're replacing the intact adult  
15 male rat assay replaces with the pubertal male and the  
16 pubertal female assay. And that's it.

17 **DR. HEERINGA:** Thank you very much, Dr.  
18 O'Connor. Questions on this? Dr. Zoeller?

19 **DR. ZOELLER:** Thomas Zoeller. So I'm a  
20 little bit confused. In the last talk the proposal was  
21 to kind of replace the amphibian metamorphosis and the  
22 two pubertal assays with this assay, and now I'm not  
23 sure that I understand whether you were --

24 **DR. O'CONNOR:** Clearly, what I'm  
25 referring to is specifically the intact male assay, so

1 I was referring to the pubertal assay. But, again, one  
2 of the strengths of this assay is manipulability to  
3 protect these thyroid-modulating chemicals, and, again,  
4 that's why in the current foundation we've added two  
5 additional thyroid-modulating chemicals in there. So  
6 the belief is, yes, it could, it could also replace  
7 the --

8 **DR. ZOELLER:** So being close wind, for  
9 example, was one that was put through this assay. It  
10 showed a decrease in T4 but no increase in TSH, and the  
11 interpretation was if TSH didn't go up, it doesn't  
12 really affect the system.

13 **DR. O'CONNOR:** Yeah. If you look at --  
14 many materials will decrease T4 due to transient  
15 decreases in T4 due to liver enzyme. Specifically, if  
16 you look at the data for this assay, of the 27 or so  
17 chemicals that have been evaluated here, if you look at  
18 T4 as a marker, I think there was only one chemical  
19 that was run in this assay during the validation or  
20 pre-validation that did not increase T4. So, again,  
21 that's why it's important to look at the way that  
22 evidence is not reliable and stable such as T4 or even  
23 just T4 and TSH. It's really important to rely on all  
24 of the thyroid endpoints that are available. So it's  
25 critical to have that histopathology to thyroid weight

as well as the thyroid hormone.

**DR. ZOELLER:** So I guess I -- I mean, I'm still -- there's a couple things that I don't understand. One is why would T4 go down if TSH doesn't up, and it's probably not transient because it's at least a 15-day sort of assay and in the other example where exposure is longer, TSH still doesn't go up. So I don't think we really understand what's happening in those kinds of situations to just make the kind of default, you know, using this idealized model that if T4 goes down, and if that reduction is important, then TSH would go up. If TSH doesn't go up, then it's not important.

**DR. O'CONNOR:** Right.

**DR. ZOELLER:** And so to just kind of finalize that, in these mammalian assays there's no measure of thyroid hormone actions. There's no tissue-related thyroid hormone action. The amphibian metamorphosis assay is really the only that does that, and there is a number of differences between amphibians and mammals that might be important to consider in a weight of evidence. So it seems to me that if you really eliminate many of the -- there's really only three assays that touch on the thyroid, and if you eliminate two of them or three of them and replace that

1 with a single assay, you're really losing a lot, at  
2 least it seems to me. And I guess my question is how  
3 do you respond to that?

4 **DR. O'CONNOR:** Right. So I think when I  
5 talk about these transient effects, really what I was  
6 talking about is the fact that if you look at long-term  
7 studies, most of the materials that we've tested in the  
8 pre-validation effort do not produce thyroid tumors in  
9 long-term rodent studies. So really that's, when I say  
10 they're transient, they don't result in tumors in long-  
11 term rodent students, and, therefore, for all effective  
12 purposes we would expect them to be negative for  
13 thyroid, thyroid disruption. With respect to the frog  
14 metamorphosis assay, I would agree with you that  
15 there's certainly a difference in what the assays are  
16 designed to do, but I believe for the most part that if  
17 you look at not only the intact adult male rat assay  
18 but the pubertal assay, they're also relying on these  
19 thyroid endpoints, thyroid weight, histopathology and  
20 hormone levels. I don't know that there are chemicals  
21 that have been run in the frog metamorphosis as we  
22 would necessarily expect to miss in these other assays.  
23 So, again, to me it goes back to the fact that if you  
24 detect it as an endocrine active chemical, specific for  
25 thyroid, regardless of how you're picking that up, is

1 it really important in a tier-1 screen as long as  
2 you're picking it up as a thyroid-modulated chemical?  
3 But, again -- so that's kind of how I would respond to  
4 that.

5 **DR. HEERINGA:** Other questions for  
6 Dr. O'Connor? I would like to thank you very much.  
7 Again, thank you to everyone. The quality of these  
8 presentations all around has been very good. At this  
9 point I'd like to ask Dr. Lisa Ortego, who is  
10 representing CropLife America to come forward, please.

11 **DR. ORTEGO:** Good afternoon. I need to  
12 add my thanks to the thanks of everybody else, to EPA  
13 and the panel for allowing us to make public comments  
14 on the assays and batteries today. I'm going to  
15 continue discussion with the comments on the amphibian  
16 metamorphosis assay and it's inclusion in the tier-1  
17 battery.

18 I want to add some questions. I want to  
19 follow what John O'Connor was just talking about was do  
20 we need a frog assay in tier-1? First of all some  
21 questions that are really pertinent to tier-1 assay.  
22 Is it rapid and is it cost effective? The frog  
23 metamorphosis assay requires 21 days in order to run,  
24 and if you run a control in four doses, which was what  
25 was previously proposed, it takes 400 vertebra and

1 about 100,000 US dollars to perform that test. Now I  
2 do understand that the current proposal by EPA is to  
3 drop one of the doses, so that would bring it down to  
4 about 320 animals and about \$80,000 to perform.

5 Does it identify the mode of action,  
6 which is important for us in tier-1? Can it identify a  
7 thyroid-active substance? The thyroid histopathology  
8 in the amphibian metamorphosis assay does indicate a  
9 mode of action, but the endpoint is already available  
10 from the rodent assays that are proposed for the tier-1  
11 in addition to the intact male, which a number of  
12 colleagues are proposing to replace pubertals.

13 Are the results straightforward to  
14 interpret? Thyroid histopathology is by a qualified  
15 individual. Rodent development effect can be  
16 confounded by compounds that cause sublethals for  
17 growth and development, and lab variability also has  
18 been an issue, especially with developmental stage.

19 Does the inclusion of this assay address  
20 concerns regarding animal usage? Well, because of the  
21 large number of animals and the fact that the data  
22 that's collected, or at least the very specific data  
23 that's collected is available for some of the other  
24 assays, I would say no. It seems a bit redundant to  
25 have such a large, a lot of animals required and a

1 costly assay to be included when other rodent assays  
2 already in tier-1 might fly compounds as thyroid  
3 active.

4 I put together a table, and,  
5 unfortunately, you're not going to be able to read a  
6 lot of it. But essentially this is to compare the  
7 thyroid activity in a rodent and in the amphibian  
8 assays. At least the compounds for which equivalent  
9 data is available, and here I have primarily focused on  
10 thyroid histopathology. And I have included the  
11 compound PTU, T4, and phenobarbital. Perchlorate also  
12 is available across rodent and amphibian assays, and  
13 there was a presentation earlier today that did show  
14 that thyroid histopathology was consistent between  
15 rodents and amphibians for that chemical. As you can  
16 see, we've got a test guideline 407 which is actually  
17 an OECD rodent guideline, the intact male assay, the  
18 female pubertal, the male pubertal, and then the  
19 amphibian metamorphosis assay histopathology. And as  
20 you can see if you read across for PTU, all of these  
21 assays were positive for thyroid activity, and it  
22 picked up essentially the same histopathological  
23 finding. For T4, in the scope of these validation  
24 exercises only the TG407 use T4, but it picked up, it's  
25 pathology picked up on a thyroid active material, where



1 as the amphibian assay histopathology was not quite as  
2 conclusive. For phenobarbital, that caused a little  
3 bit of trouble in most of the assays. In some cases  
4 they don't think the MTD was achieved. In the frog  
5 assay as well they had contradictory response there.  
6 In the intact male, it would have flagged thyroid as  
7 positive, not necessarily based on histopath but based  
8 on thyroid hormone findings and thyroid weight. So you  
9 can see that phenobarbital wasn't necessarily a good  
10 test model for this particular one. And as I  
11 mentioned, perchlorate also was equivalent across all  
12 the assays. This information is presented in, I think,  
13 in more detail in written comments that you should have  
14 available.

15 I wanted to mention too, this morning we  
16 talked a little bit about iopanoic acid and the very  
17 interesting finding of its asynchronistic development  
18 in frogs. Well iopanoic acid had not been tested in  
19 any of these rodent assays for validation. So I can't  
20 give you a comparison of that. What I know is it can  
21 cause thyroid hormone changes in humans, whether the  
22 rodent assays will pick that up I can't answer cause it  
23 hasn't been tested. It's a little bit unfortunate we  
24 don't have a larger suite of compounds that were tested  
25 across all the assays to do a more full comparison.

1 So continuing with some questions about  
2 inclusion in tier-1, is the method sensitive? Yes.  
3 Amphibian metamorphosis assay does appear to be  
4 sensitive, especially for the strong agents. It has  
5 not been as effective for the weak agents. Substances  
6 like benzophenone-2 may also have been tested at doses  
7 that resulted in non-specific toxicity based on  
8 findings in the test itself and in some fish data that  
9 indicates that those concentrations may have been a  
10 little high.

11 We can also say that we have not tested  
12 enough substances to determine the limits of  
13 sensitivity and specificity for this assay. We need  
14 more weakly acting thyroid substances and more non-  
15 thyroid toxicants to be evaluated to really understand  
16 the limitations and the strengths of the amphibian  
17 metamorphosis assay. I do have a concern that if we're  
18 looking at endpoints strictly based on growth and  
19 development, that we may have potential to flag a lot  
20 of false positives with the amphibian metamorphosis  
21 assay. And as you've already heard, for us to trigger  
22 tier-2, and my understanding from this mornings  
23 conversation was we'd probably be doing everything in  
24 tier-2 based on positive tier-1 findings. We're  
25 talking about millions of dollars and lots, and lots,

1 and lots of animals. It's an avian two generation  
2 assay. It's a fish two generation assay. It's an  
3 additional rat reproduction assay. So there's lots of  
4 work into it too.

5 Has it been sufficiently standardized? Well  
6 the results can be confounded, and they're  
7 inconsistent; sometimes within labs, and not specific  
8 for a lab, and across labs. And it's thinking that  
9 animal dye and iodine content in the water may play a  
10 part of this, but it's not fully understood how those  
11 factors will effect a response to a testing agent. So  
12 we really need some more work to really define the  
13 conditions in which the assay should be performed  
14 across laboratories, not just what the minimal dye and  
15 iodine should be but a real understanding of how those  
16 components with interact with the test substances or  
17 effect the results of the test substances. Also in  
18 some experiments the animals were developing and  
19 reached metamorphic climax already by day 21, which  
20 almost makes the data un-interpretable.

21 We need performance criteria for growth and  
22 development, and there are some performance criteria  
23 that are proposed in the integrated summary report.  
24 But I think they don't go far enough. I think we need  
25 to have more performance criteria for development

1 throughout the assay, so what stage should controls be  
2 approaching plus or minus day seven as opposed to just  
3 what the minimum they should be at, at day 21. That  
4 would help us a little bit more than interpretation for  
5 synchronicity of the development of the eggs.

6 As I mentioned, overt toxicity can confound  
7 specificity of the assay, and we need clear  
8 recommendations about how to determine when that  
9 toxicity is interfering with our interpretations. I  
10 also heard this morning that mortality will be the  
11 clear indicator for overt toxicity, but we all know,  
12 sublethals can also affect growth and development. And  
13 if we can have a growth and development effect trigger  
14 a positive finding, I see the potential for a lot of  
15 false positives here.

16 It's a challenging assay to run. We've had  
17 some experience with it at our own laboratories, and  
18 without sufficient standardization, it's going to be  
19 difficult to transfer this to laboratories to be able  
20 to run this regularly, reliably for all the compounds  
21 that must be screened.

22 So to summarize, I want to say there's been a  
23 lot of very good work on this assay. It has come a  
24 really long way. You see clear improvements from  
25 phase-1 validation, to phase-2 validation, to phase-3

1 validation. However, I don't think it's quite there,  
2 and I'm really concerned about the conclusion in tier-  
3 1. It is a long assay, as I mentioned it is 21 days.  
4 It requires a lot of animals and a lot of money to  
5 perform. It doesn't seem to give us a lot more  
6 information than the rodent assays, and if you're using  
7 tier-1 to say the compound is thyroid active, we can  
8 probably get that with another test. It doesn't  
9 provide, it doesn't work well for the weakly active  
10 agents, and we have a little trouble with consistency  
11 between and within laboratories. We need some  
12 additional work to address husbandry, and we need to  
13 understand the weak thyroid substance activity and what  
14 negative thyroid substances are going to perform like  
15 in this assay. Concern again about the false  
16 positives, and you heard about the cost for tier-2.  
17 However, that said, we don't want to ignore the  
18 amphibians in this screening program. What the  
19 recommendation or what we would like to do is look at  
20 not including the amphibian metamorphosis in tier-1.  
21 Relying on the rodent data to trigger thyroid activity,  
22 and then doing, in tier-2, using amphibians to do a  
23 quantifiable risk assess, or data that can be used in a  
24 quantified risk assessment to fully evaluate the impact  
25 in the environment. Thank you.

1 **DR. HEERINGA:** Thank you, Dr. Ortego.

2 Questions from the panel members on amphibian assay  
3 from Dr. Ortego and her presentation? Yes, Dr. Furlow.

4 **DR. FURLOW:** Just one question. So just  
5 to reiterate what Dr. Zoeller was saying earlier,  
6 actually in my work it's gratifying to hear that you  
7 think that the mammalian xenopus is identical in terms  
8 of thyroid responses and things like that. So that's  
9 actually kind of nice. The trouble is that there isn't  
10 really a receptor-based screen in any of these assays  
11 besides the amphibian metamorphosis, which was pointed  
12 out. Are you aware, do you know of industrial or other  
13 kinds of efforts to have say a thyroid hormone receptor  
14 binding assay, transactivation assay? If those things  
15 were in place conjunction with the intact rodent  
16 assays, would that make you feel more comfortable, I  
17 guess, with this kind of an approach?

18 **DR. ORTEGO:** I guess I just want to  
19 clarify that I'm not saying they're identical. I'm  
20 saying that the data that we have so far suggests that  
21 the rodent assays would have picked it up. Admittedly,  
22 we've not tested as many of those as we should across  
23 the animals, and to my knowledge are not on a receptor  
24 binding assay there. But if the rodent assays will  
25 flag it in tier-1, then do we need to do frog testing

1 in tier-1, or can we do more thorough frog testing in  
2 tier-2, which is what the plan is? And I do think  
3 there's a roll for the frogs in tier-2, just not sure  
4 about tier-1. I think we need more data to make that  
5 call. I would like to see us postpone that until we  
6 had more data.

7 **DR. HEERINGA:** Dr. Cooke?

8 **DR. COOKE:** Gerald Cooke. The water  
9 that the frogs are in, where did it come from and is it  
10 tested?

11 **DR. ORTEGO:** The dilution water that's  
12 used in the assays, it comes from a, it's usually local  
13 water that may be reverse osmosis treated and then  
14 media added to it in order to make the animals thrive  
15 and be happy. It is only screened usually for the  
16 standard pesticide screen and an organic toxicant  
17 screen. So there is a screening process. Anybody who  
18 does GOP work is screening their water for those kind  
19 of contaminants, and a lot of the laboratories use  
20 local water that they further purify and then maybe  
21 modify with amendments for the animals to thrive.

22 **DR. HEERINGA:** Further questions for  
23 Dr. Ortego? Not seeing any, I'd like to thank you very  
24 much, Dr. Ortego. At this point I'd like to ask Dr.  
25 Reinhardt Fischer representing Bayer CropScience to



1 come up.

2 **DR. FISCHER:** Thank you very much for  
3 listening to my comments. My name is Reinhardt  
4 Fischer. I'm with Bayer CropScience. I'm involved for  
5 the last 12 years with the endocrine screening and  
6 testing question. My background, I'm an  
7 ecotoxicologist by training, and I'm responsible for  
8 human and environment risk assessment at Bayer. To  
9 make the challenge a little bigger for you, I'm not  
10 showing some of the slides that are in your  
11 presentation, so you have to be on your toes.

12 Background for my comments, I'm looking  
13 at the proposed EP80 assay because there's also an OECD  
14 design that is a little bit different. The differences  
15 are outlined on your slide number 11 in the very back  
16 of your document. Also I have to state that currently  
17 there's no information available on how the results  
18 actually will be used within the screening battery. We  
19 believe that the assay by itself should provide the  
20 data that can be clearly interpreted as either positive  
21 or negative for endocrine disruption because we believe  
22 that not only some agencies in this world, but  
23 especially the public, will use positive results as  
24 positive results for the compound.

25 This slide is basically the core of my

1 comment. The study design is scientifically sound, but  
2 we believe in its current design it does not fulfill  
3 the requirements for a screen for endocrine disruption.  
4 And the two key points for that are that as admitted by  
5 all the researchers that have been involved in the  
6 validation process, some of those endpoints are not  
7 specific for endocrine disruption. They could be  
8 caused by other pathways, but then the second point is  
9 that any significant effects in one or more of these  
10 endpoints should be considered a positive response. So  
11 even if fecundity alone is affected, that would be  
12 considered a positive response, and as a result the  
13 compound would be regarded as a potential endocrine  
14 disruptor.

15 Is the basic design of the assay a screen, a  
16 rapid screen? It's definitely not rapid. The exposure  
17 duration alone is three weeks. You need a two to three  
18 week pre-exposure period plus you need a time for the  
19 range finder test because normally you don't have the  
20 results for the species that you, that you need. So  
21 you need additional information to be able to perform  
22 it. Just as it's not a short test, it's also not a  
23 cheap test. It involves a lot of labor to run a flow-  
24 through system, so that long period of time requires a  
25 lot of labor. It is expensive including the analytics,

1 the histopathology, the plasma-6 steroid analysis. So  
2 it could easily run up to \$100,000 for this compound.  
3 One of the options could be to focus on the OECD  
4 endpoints alone. In doing so there may be the option  
5 of a reduction in test duration and in cost therefore.

6 I'm flipping now to slide number seven. The  
7 question asks, has the test method been sufficiently  
8 standardized? It's a question that is really open to  
9 debate, and a question that depends on what level of  
10 resolution. You're looking at the validation results.  
11 If you just want to see if all of the labs found some  
12 positive result at some concentration levels, then,  
13 yes. It has been validated. If you want similar  
14 results at similar levels, then you will see that there  
15 was considerable variability within the test results.  
16 And on the other hand the variability of histopathology  
17 and of the sex steroids measurements cannot really be  
18 assessed because both of them were only performed by  
19 one laboratory each.

20 And then, you know, kind of minor point, some  
21 of the technical aspects need to be revisited, some of  
22 the quality criteria for the test.

23 Is the test for its intended purpose  
24 sensitive? Yes. It's definitely sensitive. Actually  
25 there is no negative in the test. All the test

1 chemicals that were tested in the validation program  
2 including in the validation program at OECD were  
3 positives in this test. It found all chemicals, so  
4 it's definitely sensitive, but it's not very specific  
5 depending on what endpoints you include. And it's  
6 also, because of that, not predictive. And I admit  
7 here, you know, that really depends on the evaluation  
8 method. If it states there that any effect would be a  
9 positive result as an endocrine disruptor, then it is  
10 not sufficiently predicted for endocrine disruption.  
11 It may be good for a good productive toxin. But it is  
12 reproducible, although it may need some more work to  
13 reduce the variability.

14 Overall the design, in our opinion, goes  
15 beyond the requirements of a screen for detecting  
16 potential endocrine disruption. The biological test  
17 procedure has been adequately demonstrated. It works  
18 from the biology of the test. Some of those endpoints,  
19 I mentioned the histopathology and the sex steroids  
20 measurements, they have not been validated so far.  
21 Some of the protocol parameters need to be verified.  
22 Someone asked this morning, is there sufficient  
23 laboratory capacity. We believe there probably is not  
24 when you're looking here in the first round of the  
25 priority chemicals alone, 73 chemicals to be screened.

1 There may not be sufficient laboratory capacity for  
2 this type of exercise. And finally, last not least, we  
3 recommend to go with the OECD test methodology and  
4 focus on the vitellogenin and secondary sex  
5 characteristics alone to make the assay more handle-  
6 able. With that, I thank you for your attention and  
7 for your consideration.

8 **DR. HEERINGA:** Thank you, Dr. Fischer.

9 Dr. Lasley has a question.

10 **DR. LASLEY:** On your last point, could  
11 you tell me how many, if any of the positives were not  
12 picked up on the OECD but were picked up with the other  
13 parameters?

14 **DR. FISCHER:** I think all of the  
15 positives would be picked up by the OECD as well when  
16 you go to that level.

17 **DR. LASLEY:** Then according to what's  
18 been tested, there's no advantage to the additional  
19 parameters.

20 **DR. FISCHER:** Not for the purpose of  
21 this, of this screen. You know there could be  
22 additional parameters when you look, as across all  
23 assays and miss any reproductive effect somewhere. But  
24 for that there's no guidance developed so far, so if  
25 the test should deliver a result by itself, then you,

1 you really should eliminate questionable endpoints.

2 **DR. HEERINGA:** Thank you very much,  
3 Dr. Fisher. At this time I'd like to invite up Dr.  
4 Steven Levine from Monsanto.

5 **DR. LEVINE:** I'd like to first start off  
6 by thanking the panel as well. And, again, I'm Steve  
7 Levine, and I'm a ecotoxicologist and a science fellow  
8 at the Monsanto Company and had the opportunity to be  
9 involved with providing guidance as well to EPA between  
10 2004 and 2006 as a member of the EDMBAC. What I'm  
11 going to talk to you about today are recommendations  
12 and considerations for the tier-1 battery.

13 So I'm going to over a little bit of  
14 ground that Gary covered earlier today, and I'm going  
15 to talk a little bit about the origins of the endocrine  
16 disruption screening program. And as you heard  
17 earlier, it really came into fruition through the  
18 enactment of two pieces of legislation. FTPA and an  
19 amendment to the Safe Drinking Water Act in 1996. So  
20 what the FTPA stipulated was that EPA must screen  
21 pesticides for estrogenic effects that may affect human  
22 health. The EPA must use appropriate validated test  
23 systems, much of what we're talking about today or  
24 other scientifically relevant information to assess the  
25 potential for endocrine activity. And EPA can conclude

1 that other effects beyond estrogenic effects could be  
2 included, and we're talking about androgen thyroid and  
3 the potential effects on steroidogenesis as well. The  
4 Safe Drinking Water Act amendment allows EPA to screen  
5 drinking water contaminants to which substantial  
6 numbers of person are exposed.

7           So you can see that the program is very  
8 large, and to help EPA develop the program, they  
9 brought in a number of advisors, as we heard earlier,  
10 academics, industry, governmental organizations to  
11 develop the framework, and that was broken up into  
12 three primary pockets, which was priority setting,  
13 screening, and if activity was identified in screening,  
14 you could be triggered to be go on to testing. We also  
15 heard that the approach on priority setting changed,  
16 and it went from using biological effects information  
17 such as the results from high throughput screening to a  
18 qualitative exposure-based analysis on relative  
19 exposure. We heard about those four routes of  
20 exposure.

21           I'd like to talk a little bit about  
22 selection criteria for assays in the tier-1 battery,  
23 and those assays should be motive-action based to  
24 identify specific types of endocrine activity. These  
25 assays should be broadly predictive. In other words



1 they should have the appropriate sensitivity and  
2 specificity. They should produce data that can be  
3 clearly interpreted as being either positive or  
4 negative to the best of the abilities, and attempts  
5 should be made to minimize type-1 and type-2 error  
6 rates. We heard about a biased towards minimizing the  
7 type-2 error rates or the false negatives, but we don't  
8 want to do that at the expense of dramatically  
9 increasing type-1 error rates. There are currently  
10 about 10 assays in the EPA proposed tier-1 battery. If  
11 each of those assays has a 5% to 10% false positive  
12 rate, when you look at the chance of finding one false  
13 positive in that battery, the percent is relatively  
14 high. It can be as high as 50% to 60% percent  
15 depending on how many assays are included in the rate  
16 or the chance of a false positive.

17 As we have just heard, the assays should  
18 be relatively inexpensive, quick and easy to perform to  
19 really meet the requirements of a screen.

20 I would like to talk a little bit about  
21 assay validation as well as battery validation, and  
22 through your deliberations over the next two to three  
23 days, you're going to be talking a lot about whether or  
24 not each of the individual assays are validated. And  
25 two of the criteria you're going to have to evaluate

1 against are relevance as well as reliability with  
2 relevance being can the assay identify a compound that  
3 has potential endocrine activity? And the other one is  
4 reliability. Are assays reproducible within a lab and  
5 between labs? Are they robust and are they portable?

6 This is an important to make. Assays in  
7 a proposed battery were not tested during the  
8 validations with the same standard set of core test  
9 substances, and this was something that Ed Stack had  
10 spoken to in their guidance document, the relative  
11 importance of this. Because with this head-to-head  
12 comparison, it's difficult to select the optimal  
13 battery. It's difficult to make apples to apples  
14 comparisons of sensitivity and specificity among the  
15 assays looking at similar endpoints, and they felt that  
16 the assay could not be considered to be properly  
17 validated unless you had this same standard set of core  
18 substances tested across the battery.

19 Another point that I want to make before  
20 moving on is the insufficient number of negative  
21 compounds that have been tested during method  
22 validation. Many of the compounds that go through  
23 testing ought to be negative. Therefore, it is very  
24 important to challenge each of the assays in the  
25 battery with a sufficient number of negative compounds

1 to really have a good understanding of specificity.

2 Another important topic that's been  
3 talked about earlier this afternoon is dough setting,  
4 and the reason for this is because dough setting takes  
5 a considerably greater importance in the screening  
6 program than in traditional toxicity testing. The  
7 purpose of screening is to identify the potentials that  
8 interact with the endocrine system not merely to  
9 identify adverse effects. So it's critical to assure  
10 that systemic toxicity or a stress response is not  
11 confused with genuine endocrine mediated effects, and  
12 this is particularly important because many of the  
13 mammalian assays are pushing the doses up to or above  
14 potentially the maximum tolerated dose.

15 Feedback that EPA specifically asks for  
16 in the FR Notice was comments on the limitations of the  
17 assays in the proposed battery, and as you've heard  
18 through the course of the afternoon, key limitations of  
19 the proposed battery are related to the number of  
20 assays that include equal endpoints. And concern stems  
21 in large part from the lack of specificity of several  
22 of the endpoints in these assays, and the concern again  
23 was generated out of the high probability of getting  
24 false positives at an exceptionally high rate out of  
25 these assays. Some of the examples that we've heard

1 talk about earlier this afternoon included the  
2 pubertals, the fish reproduction screen, and the  
3 amphibian metamorphosis assay. In the second slide I  
4 talked about FQPA and some of the mandates under FQPA,  
5 and some of the wording was that other scientifically  
6 relevant information could be used to assess the  
7 potential for endocrine activity. It is important to  
8 point out to the folks in the panel here that many of  
9 the compounds in the draft screening list of 73 have  
10 undergone extensive testing that's capable of detecting  
11 effects, endocrine-mediated effects. We're talking  
12 about higher tier apical tests. So this is a time to  
13 urge EPA to be flexible in determining which, if any,  
14 screens need to be performed based on the availability  
15 of functionality equivalent data, and we heard from  
16 Willie Owens about the prediction model and very  
17 similar predictions between uterotrophic Hershberger  
18 results from rat 2-gen studies. So there's good  
19 alignment there.

20 Another topic we've heard a fair amount  
21 today is use of a weight of evidence approach to  
22 determine the results of tier-1 screening, and the FR  
23 note is for the meeting we're attending today. EPA  
24 laid out the relevance and the importance of using this  
25 weight of evidence approach, and the rationale for that

1 is the battery will likely produce a database with a  
2 unique ray of results for individual compounds. So we  
3 really need a weight of evidence approach to evaluate  
4 this type of information, the quality of the  
5 information in a way that explicitly addresses the  
6 qualitative differences in the information. So I'm  
7 asking that EPA develop standardized and transparent  
8 recommendations, taking it to the next step to apply  
9 weight of evidence approach to determine if tier-2  
10 testing is necessary. Ideally it would be nice to have  
11 this guide, these recommendations before tier-1  
12 screening initiates and certainly before tier-1  
13 screening is completed.

14                   This is a variation of a slide you've  
15 seen earlier today in presentations. On the left  
16 column we're seeing the assays that can potentially be  
17 in the tier-1 battery. In the center column is the  
18 March 2008 EPA proposed tier-1 screening battery, and a  
19 recommended tier-1 screening battery on the far right  
20 column. One of the major differences between these two  
21 screening batteries is using the intact male to replace  
22 steroidogenesis, the pubertal male and female as well  
23 as the frog metamorphosis for reasons that you've heard  
24 earlier today. Another difference is the  
25 recommendation for only using ER binding assay versus

1 the ER binding in the transcriptional assay. The ER  
2 binding assay can detect agonist as well as antagonist.  
3 The ER transcriptional assay can only detect agonist.  
4 So the recommendation is for that ER binding assay.  
5 Additionally we just heard a presentation on the fish  
6 reproduction screen, and the recommendation there is to  
7 harmonize with the OECD protocol, which looks at two  
8 endpoints, which are very predictive of endocrine  
9 activity, vitellogenin induction as well as changes in  
10 secondary sexual characteristics.

11 So to close, I just wanted to provide  
12 some additional rationale for this recommended tier-1  
13 screening battery. The proposed battery is mechanism  
14 of action based. It's efficient and satisfactory in  
15 evaluating estrogen, androgen, and thyroid activity, as  
16 well as potential effects of steroidogenesis. It is  
17 believed to have greater predictively, and that is  
18 driven by the greater specificity of the proposed  
19 assays to include in this battery. It maximizes  
20 interpretation while minimizing the chance of type-1  
21 error rates, and overall it has a decreased complexity  
22 which is consistent with a screening battery. So with  
23 that I'll end and take any questions.

24 **DR. HEERINGA:** Thank you, Dr. Levine.

25 **DR. LASLEY:** I'm Dr. Lasley. You

1 indicated that the estrogen transmission assay could  
2 not measure antagonist. I assume you meant hasn't been  
3 validated to.

4 **DR. LEVINE:** Yes. Yeah. That's  
5 correct. It has not been validated to detect  
6 antagonism. I think there may be plans to build on the  
7 validation looking at agonist.

8 **DR. HEERINGA:** Dr. Brown?

9 **DR. BROWN:** Terry Brown. So if you were  
10 in a position of having to assign weight of evidence,  
11 some kind of quantifiable way of assessing that, can  
12 you express any perspectives on that?

13 **DR. LEVINE:** Yes. Let me start with, we  
14 did hear some comments on that earlier today. Clearly  
15 in-vitro assays cannot be the gatekeepers. Likely  
16 would assign greater weight to the in-vivo assays over  
17 the in-vitro assays. But that would be the high level  
18 of guidance. Clearly we're going to have to interject  
19 expert judgment, and I would really point towards some  
20 of the guidance that's been developed for similar  
21 weight of evidence framework, specifically the type of  
22 weight of evidence framework that we use for  
23 immunogenicity and carcinogenicity testing. A lot of  
24 these rules for weight of evidence have been, have been  
25 really pushed on and discussed to a great extent with



1 developing frameworks for those endpoints.

2 **DR. HEERINGA:** Dr. Vandenberg?

3 **DR. VANDENBERGH:** Yes. I wonder if you  
4 could explain to me how the adult male 15-day test  
5 replaces both the male and the female pubertal test,  
6 especially the female test. We have an animal that  
7 cycles. Males don't cycle. That's the basic  
8 difference between the sexes, and how do you, how do  
9 you look at the effects on cyclicity if you don't make  
10 any measurements?

11 **DR. LEVINE:** This is -- being a  
12 screening assay and being mechanism-of-action-based, I  
13 guess I would refer back to that approach for  
14 screening. I'd refer -- being a mechanism-of-action-  
15 based approach, I guess there would be some questions  
16 with the pubertal assay and Estro-cycle in whether the  
17 duration of the current study is sufficient to really,  
18 really assess that.

19 **DR. HEERINGA:** Thank you, Dr. Levine.  
20 At this point I'd like to ask our next public  
21 commentor, Dr. Ellen Mihiech. Hope I'm pronouncing  
22 the last name correctly. Okay.

23 **DR. MIHIECH:** I've learned over the  
24 years not to worry about that too much.

25 **DR. HEERINGA:** I need my earring aide.

1 **DR. MIHIECH:** I too want to thank you all  
2 for being willing to sit here and listen to all of us.  
3 I appreciate that. My name is Ellen Mihiech, and I'm  
4 an environmental toxicologist/risk assessor. I have  
5 been an interested observer and a stakeholder since the  
6 inception of this program in 1996. I've also been an  
7 active participant because I am on -- I'm a  
8 representative to the OECD echo validation management  
9 group. So I've been very involved in accepting the  
10 studies from the environmental side.

11 What I wanted to talk about, it's very  
12 similar to what Dr. Levine talked about and that's that  
13 the purpose of the screening battery and what is this  
14 purpose? We've got lots of studies that we've looked  
15 at. We've learned a lot over these years, and I do  
16 commend the efforts of the EPA, and industry, and  
17 others that have been involved, academics, in where  
18 we've taken the science here, and I think it's been  
19 very good. But we do have certain requirements for  
20 doing this, and that is that it has be validated. It  
21 has to be specific, and we have to keep in mind that  
22 this thing that you're talking about today is the  
23 screening level. We don't have to answer every  
24 question. That would be something that we would be  
25 doing more in the risk assessment part of this. This

1 is just screening. It's not hazard even. It's just  
2 screening. It's do we trip a trigger. So it's to  
3 identify substances with a potential to act, and act on  
4 one or more of the components of the endocrine system.  
5 And with this we've got to be sure that we can say we  
6 have things that act, and we have things that don't  
7 act. And I hope that you've heard through the talk  
8 these last few talks that we've got some issues there.  
9 We've got a lot of these studies that are these screens  
10 that have a tendency to probably hit just about  
11 everything, and there are some pretty significant  
12 ramifications if that happens.

13                   So I know it's been mentioned by a  
14 couple of speakers, but all these experts that have  
15 spoken to you so far have been part of a group that  
16 have provided very detailed written comments. And I  
17 really would encourage you to be sure to look at those  
18 because it's people that have taken the time to be part  
19 of the design of these studies, whether or not these  
20 studies are standardized, validated. What are the  
21 strengths? What are the weaknesses? And these are  
22 people that have been involved since day one, so they  
23 know the progression of how things have gone, and the  
24 pitfalls that we've fell into, and those that we've  
25 climbed back out of. So I think it's very important

1 for you to give that some time to read that.

2 And, unfortunately, again, having been  
3 involved for so long on this that there are things that  
4 we're looking at that do lack specificity and will not  
5 lead to interpretation; that are consistent with what  
6 the EDSP objectives are, and that's to screen and  
7 identify things that interact with the endocrine  
8 system. And, again, I want to just bring up the three  
9 that I think are the most problematic, the pubertal  
10 assays, the amphibian metamorphosis, and I'm specifying  
11 this here as EPA's proposed fish reproduction screen  
12 because it is different than the OECD screen that we've  
13 worked for a really long time to get moved forward  
14 within the OECD. So problems with the pubertal assays.  
15 I think as Dr. Marty said earlier, you see that there  
16 is definitely some issues with specificity on this  
17 assay. They're apical endpoints that respond to both  
18 endocrine and non-endocrine modes of action, and that's  
19 a problem because if they do that and we can't  
20 adequately address that or piece that out, then  
21 everything that trips a trigger here is going to go on  
22 to tier-2; and we've heard that already too.

23 There is only two dose levels, and the high  
24 dose has to be at the NDT to be interpreted as  
25 adequate, and I think you've seen from the data that

1 was presented earlier that pretty much nothing with the  
2 5% to 10% decrement in body weight gain is going to be  
3 a negative. Nothing is.

4           With the amphibian metamorphosis assay, we  
5 really haven't shown specificity, except for maybe the  
6 histopathology endpoint there. This is one that's been  
7 very central in activities within the OECD also. It  
8 has had a lot of work that's gone on with it. Again,  
9 there's apical endpoints in this assay that respond to  
10 both endocrine and non-endocrine modes of action. And  
11 I think as Dr. Ortego brought up earlier, I think it's  
12 pretty clear that, again, when you think about the fact  
13 that this is a screen and we just want to trip a  
14 trigger, we just want to say should it go on or  
15 shouldn't it go on, the data today is showing that the  
16 rat studies would do it. And it is extremely  
17 expensive. It is extremely complex, and it uses an  
18 awful lot of animals. So I encourage you to think  
19 about that. I know the question came up earlier is  
20 this a, are you here to add things to it, or keep it,  
21 or take it away. It is probably keep it or take it  
22 away, but it is to really think about. What do we need  
23 that's going to answer the question about is this  
24 compound one that should be further evaluated in the  
25 two generation studies that are going to be part of

1 tier-2, which you don't get to talk about today too  
2 much I guess.

3 And the third, the third assay, the fish  
4 reproduction assay, again, the thing that I really hope  
5 that we can think about here is that within the OECD,  
6 which you act as a signature to, there is an assay that  
7 is moving forward. It has gone through peer review,  
8 and there have been a lot of very focused fish people  
9 sitting around tables that have said the vitellogenin  
10 and the secondary sex characteristics are good ones.  
11 They can tell it's a lot, and the other components that  
12 are in the current EPA reproduction screen are not as  
13 validated. There's a lot of play in the data, a lot of  
14 inconsistencies, and maybe in the future these could be  
15 things that we might consider. But today it's not and  
16 that's why OECD has dropped those from the current fish  
17 screen, the 21-day fish screen that OECD is going  
18 forward with. And it's the same kind of thing. Right  
19 now with all the apical endpoints in the fish study,  
20 there is very few that are going to be negatives.

21 You've seen this over and over. Just again,  
22 we need to keep in mind what types of methods and what  
23 these screens need to be, relevant, reliable,  
24 sensitive, specific, graphic, cost effective, all those  
25 things, and they need to cover estrogen, androgen, and

1 thyroid responses without a lot of redundancy. Again,  
2 if we, if this is a battery that's validated, then we  
3 should be comfortable in saying if we have a compound  
4 it will be tripped if it's going to effect the  
5 estrogen, androgen, or thyroid. And we need to think  
6 about utilizing animal tests wisely.

7           So the recommended battery that Dr. Levine  
8 just talked about was ER binding. Currently the  
9 transactivation is not validated. Maybe in the future  
10 it could be something that we could consider as being  
11 useful to the uterotrophic. The intact male, I think  
12 that is something that I know you guys are -- I don't  
13 believe it's something you're considering, but I hope  
14 you do think about it because it has been, a lot of  
15 compounds have been tested in it. It combines a lot of  
16 different endpoints, and it's been very useful. The  
17 fish screening assay, but I'm recommending the OECD  
18 screen assay, the AR binding, Hershberger, again the  
19 intact male, and the OECD fish screening, and then for  
20 thyroid the intact male.

21           In closing, I just want to say remember that  
22 we need to find that appropriately focused tier-1  
23 battery that's for screening, that's going to be  
24 finding the compounds but is' going to be mechanistic  
25 based and will inform for tier-2 testing. As Dr.



1 Levine said, we need to think about the weight of  
2 evidence and how we're going to use the data. It was  
3 very troubling for me to see the materials you got with  
4 the fish reproductive screen that said any positive in  
5 any of those endpoints is a positive. That just goes  
6 counterintuitive to what this program was about, which  
7 was to look at estrogen, androgen, and thyroid. And we  
8 need to make sure that it meets within the regulatory  
9 authorities, that there's communications about the use  
10 of the data and it's consistent agency wide. So that,  
11 again, this is screening. It's not hazard. It's  
12 certainly not risk and that we need to be very careful  
13 about what we, how we use the data. Thanks.

14 **DR. HEERINGA:** Thank you, Dr. Mihiech.  
15 Questions? Yes, Dr. Kullman.

16 **DR. KULLMAN:** Hi. I think the last  
17 three speakers have some pretty valid points with  
18 trimming the assays. One of my concerns with your  
19 points though is that if we trim this too much we're  
20 going to lose some of the inherent redundancies that we  
21 have in these assays which allows us to make a defined  
22 definition of what some of these compounds might be  
23 doing. So I agree maybe we can trim some of the fat,  
24 but to trim it too much may really dent the ability to  
25 make a definitive answer on some of these.

1 **DR. MIHIECH:** I certainly understand  
2 that and I agree. I guess, again, if we had say, for  
3 example, a thyroid assay that was just perfect that  
4 didn't have a lot of the other problems associated with  
5 it, then maybe it would be okay to say all right we'll  
6 do a specific thyroid assay in the intact rat. But the  
7 problem we run into is if you think about, for example,  
8 the amphibian metamorphosis assay, if you really go in  
9 and look at the data from all the of the validation  
10 efforts that have gone on across the globe, because  
11 it's been a global program, some of those endpoints are  
12 just not there yet. I'm not saying they couldn't be,  
13 but they're not there. And so I would rather error on  
14 the side of assay that I can trust than one that I'm  
15 not going to understand how to answer the question.

16 **DR. HEERINGA:** Thank you, Dr. Mihiech.  
17 At this point in time I would like to call up -- and  
18 I'm going to guess at the last name here -- Christy  
19 Stoic, Stoic. Stoit is representing the Physician's  
20 Committee for Responsible Medicine.

21 **MS. STOIC:** It's just Stoic just like  
22 you announced it. I don't have a handout or a  
23 Powerpoint presentation. I just have some notes that  
24 I'm going to read. I'm going to make copies of those  
25 and pass them out to you tomorrow, so you will have

1 that in hard copy.

2           So PCRM is a group of physicians,  
3 scientists, and lay persons who advocate good  
4 nutrition, preventative medicine, and apical research,  
5 including use of alternatives to animals and toxicity  
6 testing. I would also like to turn your attention to a  
7 set of written comments submitted by Dr. Katherine  
8 Willet of People for the Ethical Treatment of Animals,  
9 which, along with PCRM and several other stakeholder  
10 groups. I just want to make a few short points today.  
11 The first point is I hope the EPA will take this as  
12 constructive criticism, but it was really hard to  
13 prepare for this meeting. Not only were there tons and  
14 tons of documents, but they weren't all in one place.  
15 I wasn't really sure which documents to focus on. They  
16 weren't on the public docket in advance of the deadline  
17 for written comments. There was a really nice summary  
18 that was made available after the deadline for the  
19 written public comments, so the technical review  
20 document; that's what I'm talking about. And some of  
21 the documents in the peer review lists and such on the  
22 EDSP website were different than what was presented  
23 here today, so I'm just asking to maybe next time try  
24 to get everything ready at least before the written  
25 comments are due.

1 So although many stick holders including  
2 my organization have at one time petitioned or urged  
3 the agency to implement the EDSP more quickly, the  
4 information presented here leaves me with the  
5 conclusion that the first tier, as proposed, are not  
6 ready for implementation. Battery assays, for example,  
7 the transcriptional activation assays are not  
8 validated. Some of the assays EPA included in the  
9 battery are not yet validated. There are also serious  
10 problems with the validation of some of the assays.  
11 It's not the time now to offer expediency over  
12 scientific validity. This program is too significant,  
13 too important, and it's going to have a huge impact.  
14 Instead, we believe EPA should endeavor to adopt a  
15 program more in line the original intent of the statue.  
16 First and foremost detect estrogen-like effects in  
17 humans using very rapid priority setting in-vitro  
18 mechanistic screens. Further tier screening and  
19 testing will be contingent on a clear stepwise process.

20 It's inconvenient for the agency to  
21 adopt a more flexible approach to assay validation for  
22 this program. This is not appropriate. It does not  
23 follow that because these assays are not replacing  
24 another assay, they should be subject to less vigorous  
25 validation. If anything, the validation process should

1 be more rigorous because neither the biological  
2 flexibility or some of the assays nor determining a  
3 positive and negative cause is immediately apparent.  
4 One limitation of many of their validation studies in  
5 our view, especially for the apical in-vivo assay, is  
6 there is a posse of chemicals tested in the validation  
7 sites that are toxic but not endocrine disrupting.  
8 This would essentially be relevant as we've heard in  
9 assays such as the amphibian metamorphosis. By not  
10 validating the assays using these compounds, the  
11 important evaluation of specificity of the assay is  
12 being left out.

13 And finally we would like, we recommend  
14 the agency set an acceptable level of false positives  
15 before it begins evaluating the battery instead of  
16 after the fact, and it's equally important to minimize  
17 the potential for false positives.

18 **DR. HEERINGA:** Thank you very much,  
19 Ms. Stoic. Any questions from the panel? Thank you  
20 very much.

21 **MS. STOIC:** Thank you.

22 **DR. HEERINGA:** At this point I'd like to  
23 call forward Dr. John Gordon who is here representing  
24 Xenobiotic Detection Systems in Durham, North Carolina.

25 **DR. GORDON:** Hello. I'm John Gordon

1 from Xenobiotic Detection Systems, Director of  
2 Research. I'd also like to thank the panel for  
3 allowing us all to come here and speak with you today.  
4 Here we go. Today I'd like to talk to you about the  
5 Lumi-Cell ER assay developed by our company for  
6 estrogenic testing of endocrine disruptors. Well about  
7 the assay, it is a transcriptional activation assay,  
8 which we've heard a little bit about today. It's a  
9 stable transcrepant cell line from a BG1 human ovarian  
10 carcinoma cell line and is implemented in a high-  
11 throughput format. This should be a very important  
12 aspect, especially post validation in that EDSTAC has  
13 identified some 78,000 compounds that they'd like to  
14 screen. And if an assay is not in a high-throughput  
15 format, that is going to take a considerable amount of  
16 time and expense to screen these compounds. So it  
17 should be an important aspect in any assay validation.

18 I'm going to skip the next couple of  
19 slides. I think we all understand transcriptional  
20 activation. Assay validation. The assay was started  
21 with an SBIR grant from NIHS in 1997. The system was  
22 given a high-priority validation from Sacaton in March  
23 of 2004. In April of 2004, the final report from the  
24 SBIR funding was given to ICCVAM. This included a  
25 study of over 125 compounds with both agonist and

1 antagonistic data. In March of 2004, it was approved  
2 for an international validation study with ECVAM,  
3 JaCVAM, and ICCVAM. In July of 2006, we completed a US  
4 Protocol Standardization Study also known as the US  
5 Pre-Validation Study. And in March of 2007, we did  
6 start the International Validation Study with ICCVAM,  
7 JaCVAM, and ECVAM. ECVAM was doing the study in house.  
8 It is for Italy. JaCVAM was doing the study with the  
9 Yusha Corporation in Japan and XDS is doing the study  
10 for ICCVAM.

11 Don't really look at the date on this  
12 study. It's just to give you an idea of what we can do  
13 for you as far as data. We can give you the compound  
14 and case number of course. I give you the EC50 and  
15 then we give you the relative induction to EC50. It  
16 gives you prioritization for those compounds, say beta-  
17 estradiol or to pesticide. In this instance it's  
18 chlordane, and what's your relative potency to  
19 chlordane. So it gives you a little bit of an idea of  
20 how to prioritize your efforts.

21 Now I'd like to spend a little time  
22 talking about the data that's been produced with the  
23 Lumi-Cell ER assay. This about a dozen compounds that  
24 are currently on your list of 73 that you want for  
25 validation of your studies that's already been



1 completed. This is some pesticides from ICCVAM, just a  
2 list of 78 compounds that we published in the paper two  
3 to three years ago, several compounds, well known  
4 endocrine disruptors nothing, no surprises here at all.  
5 This is actually the data from the US Protocol  
6 Standardization Study performed by ICCVAM. We had  
7 several. The one in pink on the left there is beta-  
8 estradiol, which is the standard, and it included two  
9 other strong endocrine disruptor compounds, ethinyl  
10 estradiol and dedes as well as several other weaker  
11 active compounds for the study. And this is just the  
12 summary of the agonistic portion of the study. This is  
13 a slide that several people might be interested in. We  
14 heard several speaks talk about the lack of validation  
15 of antagonistic data for transcriptional activation  
16 studies. This is the data from the US Protocol,  
17 antagonistic study performed by ICCVAM. The line on  
18 the left portion of the screen is the standard curve of  
19 raloxifene and E2. We've also included such compounds  
20 as dibenzo-(a, h)-anthracene, tamoxifen and several  
21 others, flavone for instance. We did something else  
22 with this study as well. We also looked at cell  
23 toxicity or cell viability with the study, which is  
24 very valuable for any antagonistic study that's being  
25 done. If you notice some of the lines are different

1 colored, portions to the line. In yellow, which  
2 doesn't show up very well there unfortunately, is  
3 damaged cells which will not viable, and the red  
4 portion were dead cells. This viability was conducted  
5 through both a visual inspection and using a CellTiter-  
6 Glo from Promega. The cell toxicity was evaluated by  
7 two methods. So we do know whether or not there, you  
8 see an antagonist response or cell death in this case,  
9 which is very important. If you take a look at the one  
10 line that come down. It looks like a perfect  
11 antagonistic line if I hadn't colored it in yellow and  
12 red. You'd see a false positive there if we didn't  
13 take into account the cell viability; that's a very  
14 important aspect to the study. And obviously the  
15 previous transcriptional activation assay that  
16 everybody is talking about hasn't been validated for  
17 antagonism. This one has gone through US protocol  
18 standards for antagonism and is currently involved in  
19 the international study with ECVAM, JaCVAM, and ICCVAM  
20 study.

21                   This I threw in there. We not only do  
22 compounds, individual compounds, we also look at  
23 formulations. When we're doing these studies. This  
24 happens to be a sunscreen formulation study we did  
25 looking at various sunscreens bought off the shelf and

1 looking at their estrogenic potential. We also did, we  
2 do a classification system, which may be very helpful  
3 to this committee in prioritizing efforts. These are  
4 but a few compounds that we've tested, some strong and  
5 weak compounds, and what we did was, first thing I did  
6 was I looked at, well where's the background? That's  
7 the bottom blue line you see there. That's the  
8 background of the system. The red line represents the  
9 EC50 for beta-estradiol, which is the light blue line.  
10 It's the second to the left is the estradiol, and then  
11 the top light blue line represents 100% expression for  
12 estradiol. So we classify these as group A being about  
13 100% estradiol, B being between 50% and 100%, C being  
14 between 0, background, excuse me, not 0, background and  
15 50% of estradiol expression, and with D being below  
16 background or negative, non-detects. We further will  
17 take a look at this data and notice a few groupings  
18 that we can see here. You see the group to the left is  
19 your steroids pharmaceutical products kind of grouped  
20 together, and then there's a gap in the middle.  
21 There's very few data coming up, and then you take a  
22 look to the right. There's a big group of compounds  
23 that come up as the weak actives. I shouldn't say  
24 weak. I should say less active, and even within that  
25 group, there's two groups. If you take a look at the

1 -- sorry I don't have a pointer -- there's an upper  
2 portion and then a lower portion. You'll see two  
3 distinct groups of chemicals that are coming through.  
4 So we decide, we divide that into various groups as  
5 well and get those classifications, class 1, 2, 3, and  
6 4. This will allow. This system classification will  
7 allow for prioritization going on to step 2 in the same  
8 group, group C class 4 shouldn't be given the same  
9 priority going onto to phase 2, as it would be class 3  
10 or a group A class 1. This system of classification  
11 will really help refine the process of moving onto  
12 phase 2, tier 2, tier 2, pardon me, before it moves on.

13                   And then a little summary here. It's a  
14 transcriptional activation assay. I don't believe that  
15 there is a TA assay included in the upcoming pesticide  
16 study. I could be wrong about that, but I don't  
17 believe there is one. It's very sensitive to test  
18 compounds less than 1 part per trillion. Wide range of  
19 both agonistic and antagonistic studies for IC and EC50  
20 determinations. It has been through the US Protocol  
21 Standardization and is currently going through the  
22 International Validation Study for both agonistic and  
23 antagonistic studies, and it meets requirements  
24 mandated by EPA and ICCVAM for tier-1 screening assays  
25 in that it satisfies the 3 R's that we're all very

1 familiar with.

2 And I thank you for your attention. I'd  
3 like to take any questions on Lumi-Cell.

4 **DR. HEERINGA:** Thank you, Dr. Gordon.

5 Yes. Dr. Lasley.

6 **DR. LASLEY:** Dr. Lasley, UC Davis. I  
7 noticed on your antagonist response where you're  
8 testing them against E2. There's an initial agonist  
9 afoot.

10 **DR. GORDON:** Correct.

11 **DR. LASLEY:** But then when you get to  
12 the classification, you're testing these alone and see  
13 only an agonist effect. So how do you separate these  
14 two different qualities when they're both in the same  
15 chemical?

16 **DR. GORDON:** Well the antagonistic assay  
17 is actually anti-activation assay. We activate it with  
18 E2 and then use varying concentrations of the compound  
19 --

20 **DR. LASLEY:** No. I understand that.

21 But if initially --

22 **DR. GORDON:** Mm-hmm.

23 **DR. LASLEY:** -- in the presence of a  
24 strong agonist you get an agonistic, an antagonistic  
25 effect.

1 **DR. GORDON:** Yeah.

2 **DR. LASLEY:** But alone you get an  
3 agonistic effect. How do you separate those two  
4 properties if they happen to be in the same chemical?

5 **DR. GORDON:** Some chemicals are going to  
6 have both effects. In fact, if you look at the  
7 antagonistic data, you do see dibenzo-(a,h)-anthrocene  
8 is a biphasic compound. It has both agonistic and  
9 antagonistic qualities within the assay.

10 **DR. LASLEY:** So it depends upon the  
11 concentration of the strong agonist; is that right?

12 **DR. GORDON:** Correct.

13 **DR. HEERINGA:** Dr. Denver.

14 **DR. DENVER:** What is the timeframe of  
15 your assay?

16 **DR. GORDON:** Twenty-four hours.

17 **DR. DENVER:** So you could potentially be  
18 having some non-ER dependent effects in the assay given  
19 that long timeframe?

20 **DR. GORDON:** Non --

21 **DR. DENVER:** Right. I mean, if there  
22 was a compound affecting the expression of some other  
23 gene then could it impact your reporter?

24 **DR. GORDON:** Sorry. I did skip over  
25 that. This, this is the normal transcriptional

1 activation of, within the system. We added in the ERE  
2 right in front of the luciferase gene.

3 **DR. DENVER:** Right. I understand this,  
4 but what I'm saying is that given that length of time,  
5 the reporter could be influenced by other things that  
6 are changing in the cell?

7 **DR. GORDON:** It's possible but we have  
8 not observed any non-congruence with other, with other  
9 studies. In fact, the US Protocol Standardization  
10 showed 100% congruence with foreign data, with the  
11 agonist. Only 75% congruence with the antagonistic,  
12 but the previous studies it was compared to did not  
13 take into account cell liability.

14 **DR. DENVER:** Okay. And just one other  
15 question. Have you corroborated the transactivation  
16 data with any, any endogenous test regional response  
17 genes in the cells, or do you find in activation do you  
18 see enough regulation of known estrogen response  
19 changes of these different chemicals?

20 **DR. GORDON:** I don't believe we've done  
21 those studies. We have done some studies comparing it  
22 to the uterotrophic assay and several other in-vivo  
23 assays.

24 **DR. HEERINGA:** Dr. Eldridge and then  
25 Dr. Brown.



1 **DR. ELDRIDGE:** Eldridge of Wake Forest.

2 I was going to ask, is this ER alpha in the cell.

3 **DR. GORDON:** It has both alpha and beta.

4 **DR. ELDRIDGE:** That's what I was going  
5 to ask you, or can you, can you create a construct of  
6 just data for example?

7 **DR. GORDON:** I'm sure you could create  
8 one. Yes. The receptor is an endogenous receptor, so  
9 it has both alpha and beta.

10 **DR. ELDRIDGE:** So the cell already  
11 has --

12 **DR. GORDON:** Correct.

13 **DR. ELDRIDGE:** receptors?

14 **DR. GORDON:** Correct. It's an endogenous  
15 receptor. So I'm sorry. I didn't cover that.

16 **DR. HEERINGA:** Does that cover your  
17 question, Dr. Brown? Okay. Dr. Belcher?

18 **DR. BELCHER:** Yeah. In what ERE are you  
19 using this?

20 **DR. GORDON:** I'm sorry. What?

21 **DR. BELCHER:** The ERE, the promoter.

22 **DR. GORDON:** The promoter?

23 **DR. BELCHER:** Yeah.

24 **DR. GORDON:** What's it from?

25 **DR. BELCHER:** What, yeah, which ERE.

1 **DR. GORDON:** Oh, it's a Bitta Jong.

2 **DR. HEERINGA:** Dr. Lasley?

3 **DR. LASLEY:** Lasley, UC Davis. Have you  
4 looked to see what other receptors are in here or the  
5 ability of this cell to metabolize toxicants?

6 **DR. GORDON:** No. I'm sorry. We haven't  
7 really looked at other receptors. It's a very slow-  
8 growing cell system. It does not have a very high  
9 metabolic rate at all.

10 **DR. LASLEY:** Right. But, but you could  
11 do PCR and find --

12 **DR. GORDON:** Yeah.

13 **DR. HEERINGA:** Just a note. If we're  
14 going to talk, you got to come up. Okay. Please come  
15 up and introduce yourself.

16 **DR. CLARK:** George Clark from Xenobiotic  
17 Detection Systems. Sean and I do this work together,  
18 and I did most of the cell characterization work. So  
19 he may not be aware of it, but this particular cell has  
20 functional receptors for EGF receptor, and ER receptor,  
21 an AH receptor, and it does, those have been  
22 characterized in previous work. So it's an interesting  
23 cell to say the least; that's why we selected it.

24 **DR. HEERINGA:** Why don't you remain just  
25 a second, Dr. Zoeller.

1 **DR. ZOELLER:** So how stable are these  
2 responses over passage?

3 **DR. GORDON:** They've been stable for, I  
4 believe, 10 or 15 years, 10 years?

5 **DR. CLARK:** We started this work in 1997  
6 with the SBR grant, so it's been since there. It's  
7 almost 10 years.

8 **DR. ZOELLER:** Another example, I guess  
9 I'm a little more familiar with his MCF7 cells that  
10 within a lab over even, you know, a certain number of  
11 months you can lose sensitivity to estrogen for reasons  
12 that maybe we don't fully understand, but you've never  
13 seen this kind of variability through passage number?

14 **DR. GORDON:** No. We've gone through  
15 several generations of the cells, over 20 passages and  
16 never seen a drop in signal. Kept QC charts for  
17 positive controls and all this, and everything falls  
18 within acceptable ranges. And this is in accordance  
19 with ICCVAM.

20 **DR. HEERINGA:** Are there questions from  
21 the panel members?

22 **DR. GORDON:** I'm sorry. We also don't  
23 keep cells up very long, about three months and they go  
24 down.

25 **DR. HEERINGA:** Dr. Gordon, Dr. Clark.

1 **DR. CLARK:** Well thank you. I just  
2 wanted to correct --

3 **DR. HEERINGA:** No problem. I just want  
4 to make sure we get your name for the record.

5 **DR. CLARK:** George CLARK, President of  
6 Xenobiotic Detection Systems.

7 **DR. HEERINGA:** Thanks a lot.

8 **DR. GORDON:** Thank you.

9 **DR. HEERINGA:** Thank you very much, Dr.  
10 Gordon and Dr. Clark. At this point in time I'd like  
11 to take a short break, and we have two more public  
12 presenters, each who have registered for 10 minutes.  
13 And let me just check. We have one other additional  
14 presenter who was not on my original agenda. So let's  
15 take a 15-minute break and come back here just before  
16 3:30, and we'll complete the period of public comment  
17 after the break.

18 **DR. HEERINGA:** Okay. Welcome back  
19 everyone to the final part of our afternoon session of  
20 the first day of our meeting in the FIFRA Science  
21 Advisory Panel on the topic of the Endocrine Disruptor  
22 Screening Program Endocrine Disruptive Screening  
23 Program Proposed Tier-1 Screening Battery. This  
24 afternoon we've been engaged in the period of public  
25 comment, and we have additional public commentators to

1 complete the afternoon. And at this point in time I'd  
2 like to invite up Dr. Jennifer Sass, who represents the  
3 National Resources Defense Counsel. Jennifer?

4 **DR. SASS:** Good afternoon and thank you  
5 for the opportunity to present public comments. My  
6 comments for other people in the audience should also  
7 be docketed, if not already, then soon. They have been  
8 submitted, and I think that panel members have paper  
9 copies. I won't be reading through all of them word  
10 for word. I'm going to be summarizing them, but first  
11 a bit of an introduction. My name is Jennifer Sass.  
12 I'm a senior scientist in the Health and Environment  
13 Program with the National Resources Defense Counsel.  
14 It's an environmental non-profit, and I'm located here  
15 in Washington. My background is toxicology, and  
16 molecular biology, and developmental biology, but a lot  
17 of these comments were written by my colleague who is  
18 in our San Francisco office, Dr. Sarah Jensen. She is  
19 an MD, PhD, and also Master's in Public Health, and her  
20 specialty is actually endocrine and reproductive talks.  
21 So her and I worked on these together, and in a way I'm  
22 representing her here in Washington. So I can -- if  
23 there are any questions that are very specific or  
24 anything where I begin by saying, "That's a good  
25 question," that's probably the clue that I can get back

1 to you if you'd like after talking with Sarah.

2 So first of all some general comments.

3 My organization, NRDC, has been pushing EPA to meet  
4 their deadlines, and we've even been helping them to  
5 make their deadlines. And we will continue to do so,  
6 so we have an overall concern that EPA has already and  
7 may continue to fall behind on their mandated deadlines  
8 to implement the Endocrine Disruptive Screening  
9 Program. And if the Scientific Advisory Panel agrees  
10 that the assays are relevant and valid, and if concerns  
11 can be met by the EPA easily, then we would hope that  
12 EPA could begin testing the initial list of chemicals  
13 using these assays on the current schedule.

14 Going to page two, we have some concerns  
15 about EPA's failure, that EPA's failure to implement  
16 the Endocrine Disruptive Screening Program in a timely  
17 manner has stymied both regulations and the work of  
18 public interest groups like myself. NRDC has an  
19 expertise and a long history of working on chemicals  
20 that are suspected or known endocrine disrupting  
21 chemicals, and we're often approached by legislatures,  
22 by other organizations who are interested in learning  
23 about the latest science and also about the public.  
24 And many of these people wonder what our federal  
25 government is doing to help protect the public's health

1 when considering the potential association between  
2 exposure to endocrine disruptors and human health  
3 conditions such as infertility, birth defects of the  
4 reproductive systems, reproductive organ cancers, or  
5 neurodevelopmental conditions. In addition, there is  
6 increasing public scrutiny and public concern for  
7 effects of chemical contaminants on waterways, reports  
8 of intersects fish in our nation's rivers, and concern  
9 about these kind of contaminants in the drinking water.

10           The Endocrine Disruptive Screening  
11 Program was intended to help define which chemicals  
12 could be capable of causing these effects and  
13 ultimately to provide information to protect the  
14 public's health so that regulators could spend their  
15 resources wisely to make decisions to regulate  
16 appropriately to protect public health. EPA has failed  
17 to do this, not only by delaying implementation of the  
18 testing program but also by refusing to regulate any  
19 chemicals that had been shown to be endocrine  
20 disruptors in the public literature. EPA instead has  
21 inserted stock language in all of its pesticide REDs,  
22 the re-registration eligibility decisions, and  
23 tolerance reassessments that indicate that they won't  
24 make a decision on the endocrine disrupting potential  
25 for a chemical until the endocrine disrupting screening



1 program has been implemented, even where robust data  
2 was available in the peer review public literature.

3           So EPA's failure to regulate pesticides  
4 that are established endocrine disruptors on the basis  
5 of these endpoints has resulted in continued exposures  
6 to vulnerable human and wildlife populations with  
7 perhaps adverse permanent or irreversible health  
8 effects.

9           Some specific comments on the tier-1,  
10 the fish reproductive screen. NRDC is very supportive  
11 of the fish reproductive screen. It is an important  
12 test for endocrine disrupting effects, and it is highly  
13 relevant to predicting potential risks relevant to  
14 human health. The fish assay proposed by EPA has  
15 undergone peer review, and it's found to be  
16 biologically and toxicologically relevant. For a  
17 screen for the hypothalamic-pituitary-gonadal pathways,  
18 for perturbing chemicals, particularly the  
19 antiestrogenic and antiandrogenic compounds. It is  
20 seen as appropriate for identifying endocrine  
21 disrupting chemicals, both for ecological reasons and  
22 for extrapolating to human endpoints and because there  
23 is a significant degree of conservation in the function  
24 of the HPG axis across vertebrates, the tests are  
25 relevant to predict likely endocrine-disrupting modes

1 of action in other vertebrae including humans.

2 Fish levels also offer advantages over  
3 mammalian models in that the length of the assay is  
4 shorter, less expensive as well as offering more  
5 efficient routes of chemical exposure and delivery in  
6 many cases. In my written comments I site to an  
7 article by EPA scientists who are here, Gerald Ankly  
8 and Rodney Johnson, who reviewed the use of the fish  
9 assays to identify wildlife in human endocrine-  
10 destructing chemicals. I sum up what they wrote in  
11 their article and also a number of other reviews, and  
12 they conclude that, "Both from ecological effects and  
13 species extrapolating perspectives, fish tests are an  
14 important component of the endocrine disruption  
15 chemical screening and testing programs. Partial and  
16 full life cycle tests with fish that are focused on key  
17 aspects of reproduction and development not only  
18 provide a basis for quantitative predictions of  
19 ecological risk of the EDCs to fish populations, but  
20 through consideration of endpoints that are sensitive  
21 and diagnostic for different classes of EDCs, serve as  
22 effective generalized models for identifying chemicals  
23 that affect specific components of the vertebrae HPG  
24 axis."

25 I have a personal interest in this because my

1 entire PhD and a good chunk of my post doc was using  
2 different fish assays, and every time I spoke I had to  
3 make the argument that they were relevant. I don't  
4 think I made it as strongly as their article, and  
5 that's why I'm citing them.

6 EPA should set consistent protocols and  
7 procedures for the tier-1 assays. There's a number of  
8 concerns that NRDC has, and to be honest, I think that  
9 every one of them has already been brought up, but I'll  
10 touch through them quickly. And they are in my written  
11 comments. We're concerned that EPA does not have a set  
12 of consistent procedures that apply to all assays  
13 regarding issues such as how doses will be chosen and  
14 the use of positive and negative controls. And I'm not  
15 actually going to go into detail 'cause that discussed  
16 earlier by the SAP here. There are some  
17 inconsistencies, and they will result in variability in  
18 data that will make it difficult to predict, sorry to  
19 interpret the results. Those ambiguities could be  
20 averted, we think, with some pre-thought. Also EPAs  
21 should clearly define the procedures that are going to  
22 be used to decide what doses are used in the tier-1  
23 screens. As recommended by Ed Stack, they should run  
24 the tier-1 screens over a wide range of doses that  
25 include environmentally relative doses. Utilizing only

1 high doses in the tier-1 may risk observing effects  
2 caused by phytotoxicity or modes of action outside of  
3 endocrine-mediated effects, and also effects of high  
4 doses may be different than effects at low doses, which  
5 was also brought up earlier in discussion. And  
6 finally, there are some inconsistencies, we've noticed,  
7 in the use of controls in the tier-1 screening assays.  
8 There are several assays that don't list having  
9 positive controls, and as the Endocrine Disruptive  
10 Screening Program is initiated and each screen is  
11 evaluated further, a positive and a negative control  
12 should accompany each screen. These inconsistencies,  
13 we believe, can be quickly resolved by EPA before  
14 implementing the tier-1 screening assays without  
15 holding up the work.

16 We are also suggesting for consideration that  
17 future rounds should include mixtures. It's the way  
18 people are exposed, and it's also the way wildlife is  
19 exposed in real world situations. And so considering  
20 drinking water contaminants and mixtures was  
21 recommended by Ed Stack. I think that's all I'll say  
22 on that.

23 We're also very supportive of the idea that  
24 it's an open process, that as the science develops and  
25 as new assays and new approaches are validated; that

1 they be incorporated and that there be a period of  
2 review built into the process, and that EPA have that  
3 recommendation be made to it quite clearly so that  
4 groups like mind can hold them to it.

5 Thanks very much. Are there any questions?

6 **DR. HEERINGA:** Thank you, Dr. Sass. Any  
7 questions for Dr. Sass on her presentation? Thank you  
8 very much. At this point in time I'd like to invite  
9 forward

10 Mr. Scott Slaughter, who represents the Center for  
11 Regulatory Effectiveness.

12 **MR. SLAUGHTER:** Thank you for letting me  
13 be here and talk. I'm Scott Slaughter and I represent  
14 the Center for --

15 **DR. HEERINGA:** Scott, would you use the  
16 microphone.

17 **MR. SLAUGHTER:** That working now.

18 **DR. HEERINGA:** Yeah.

19 **MR. SLAUGHTER:** Okay. Thank you. It  
20 will be better the second time. I'm Scott Slaughter,  
21 and I represent the Center for Regulatory  
22 Effectiveness. Any questions about CRE are probably  
23 best answered by our website, which is [www.DCRE.com](http://www.DCRE.com).  
24 In my case, next to last is least 'cause I'm assuming  
25 someone is coming behind me. I've been very impressed

1 with the presentations so far. My predecessors have  
2 been outstanding in explaining the criteria that are  
3 necessary for validating tests and discussing whether  
4 the EPA tier-1 battery meets those criteria. With  
5 regard to this question, we urge the SAP to consider  
6 the data Ecuadia and the ICCVAM validation criteria in  
7 review of the T1 assays. The EPA cannot use the T1  
8 assays or require that any of the assays be performed  
9 by an outside body unless the record for each assay  
10 shows that the assay beats the DQA and the ICCVAM  
11 validation criteria. These criteria are set forth in  
12 detail in our written comments, and I won't repeat them  
13 here, except to note that influential scientific  
14 information like these assays have to meet especially  
15 stringent validation criteria. Just one example, EPA  
16 has to assure the reproducibility of each assay before  
17 it can require it to be performed.

18 We also urge the SAP to consider the  
19 three R's in their reviews of the tier-1 assays. EPA  
20 has to comply with the three R's. This is mandatory by  
21 statute. It is not discretion over the agency. EPA  
22 cannot use these assays unless the record for each  
23 assay shows compliance with the three R's. Finally, we  
24 ask the EPA to identify on the public record the  
25 agency's previous summation review for compliance with

1 the data Ecuadoria and the ICCVAM validation criteria,  
2 and with the three R's. We've looked, and it's  
3 probably our fault, but we're having a hard time  
4 finding an adequate discussion in the record and  
5 identification in the record by EPA of its compliance  
6 with these requirements.

7 We thank you for the opportunity to  
8 present these comments, and we look forward to  
9 continuing discussion with the EPA. Are there any  
10 questions?

11 **DR. HEERINGA:** Thank you Mr. Slaughter,  
12 any questions? Thank you very much. We have one more  
13 individual present for public comment, and that is  
14 Dr. Katherine Willet who is representing People for the  
15 Ethical Treatment of Animals, PETA. Dr. Willet?

16 **DR. WILLET:** Thank you very much. I'd  
17 like to thank the EPA for allowing us to give our  
18 public comments. I'm Katherine Willet, and I am  
19 employed by PETA. We had recently submitted lengthy  
20 written comments on behalf of the animal protection  
21 community of North America. So for more details and  
22 examples, I'd urge you to look at those comments. I'm  
23 going to give a sort of 30,000 view, 30,000 foot view  
24 of our comments in just the introductory part. I'm  
25 actually not going to touch on the individual assays



1 much at all 'cause those have been thoroughly covered  
2 by people that are much more qualified than I am.

3 I do want to tell you a little bit about  
4 my background. For many years I was a developmental  
5 biologist. I worked with Zebra Fish, and I did  
6 teratogenicity assays in a pharmaceutical company. I  
7 also was beginning to work on endocrine screening. I  
8 did a vitellogenin assay with Zebra Fish. So I have  
9 some familiarity with the issues around screening and  
10 moderate throughput screening, and for the past year  
11 and a half I've been the representative of ICAPA to the  
12 OECD under the VMG, mammalian and VMG, non-animal.

13 So throughout my slide I put pictures of  
14 animals just to remind everyone who's doing the lion's  
15 share of the work in these assays. Of course my talk  
16 is going to be filled with critique. I hope it will be  
17 taken in the light in which it's meant, which is to be  
18 constructive.

19 There are some logical issues with  
20 reviewing this battery. I'm sorry the print is so  
21 small. First of all, not all assays have yet been peer  
22 reviewed. One has been thoroughly, has been completed  
23 validated by the OECD. However, that validation was  
24 not without its issues shall we say. Three others are  
25 in various stages of validation at the OECD and have

1 not yet been fully completed. I'm sorry. I'm using  
2 the list of assays that was in the federal register  
3 notice for this meeting, which is slightly different  
4 than the list that was presented here today. I did not  
5 include the transcription activation assay for the  
6 estrogen receptor.

7           The EPA released results of its own peer  
8 review of six assays between November of 2007 and  
9 February of 2008. So altogether we have no information  
10 regarding the validation state of the 9 or 12, I'm not  
11 sure how many, proposed assays there will be. And the  
12 agency also has not provided any explanation yet as to  
13 how the tier-1 data will be used, either for decision-  
14 making in terms of potential classification or whether  
15 or not triggers for tier-2, that sort of thing, or how  
16 the tier-1 is going to be integrated in the overall  
17 risk assessment process. So on the one hand,  
18 therefore, there is not enough information to comment  
19 with any confidence really on the battery as a whole,  
20 and on the other hand there's, in a way, too much  
21 information about each individual assay to adequately  
22 evaluate one time. We've been given a task to evaluate  
23 somewhere between 5 to 10,000 pages of material. It's  
24 kind of a lot.

25           So let's get down to the overview, the

1 organization of the tier-1 battery. Again, these  
2 numbers are a little off because they're approximate.  
3 The putative tier-1 battery contains four, possibly  
4 five in-vitro assays and eight or nine in-vivo assays,  
5 which is approximately a dozen assays. The tier-1 did  
6 not consider at all physiochemical data, existing  
7 toxicological data, or things like QSAR modeling. The  
8 relatively few in-vitro assays for tier-1 is very in-  
9 vivo heavy. It ignores a lot of the in-vitro assays  
10 that are in validation at OECD, for example the  
11 transcription activation. I'm glad that the ER  
12 transcriptional activation assay will be considered.  
13 And for some of these assays, the EPA is not using  
14 internally validated protocols, which is an issue in  
15 terms of being able to share data, applicability to  
16 other countries, and that sort of thing. For example,  
17 the OECD binding assays, which the EPA is involved in  
18 the international validation of, uses a human  
19 recombinant androgen receptor, which makes a lot of  
20 sense in terms of human relevance. Whereas the  
21 protocol that's being used by the EPA for the EDSP uses  
22 cytosol from the rat prostate. I understand the issue  
23 is primarily over intellectual property. However, I  
24 think intellectual property is going to be an  
25 increasingly important issues, especially with non-

1 animal or alternative methods, in-vitro methods, in the  
2 future and for screening programs when we really have  
3 to figure out a way to get around this as a block  
4 because it's going to continue to increasingly be a  
5 problem, I think, as the technology develops.

6 As I mentioned, the tier-1 battery is very  
7 animal intensive. I mean, potentially we talking -- I  
8 understand today we're talking about the first round,  
9 which is 73 compounds. But this program in general --  
10 this potentially talks about 10's of 1000s of chemicals  
11 to be tested in approximately a dozen different assays.  
12 Thus, based on the numbers from the assays that we've  
13 been given, each chemical would use a minimum of 186  
14 rats, 72 fish, and 320 frogs assuming no range finding,  
15 minimal controls, and each chemical is tested only  
16 once. This is an extremely unlikely scenario, and this  
17 could be the largest screening program ever proposed by  
18 the US. It requires enormous quantities of each  
19 chemical, especially the aquatic assays. If you've  
20 figure out how much the volumes are for those flow  
21 things, its staggering. Okay. These are all  
22 characteristics that are not really suitable for a  
23 screen of possibly 10s of 1000s of comments. A more  
24 official approach would be to take into account the  
25 physiochemical date and all preexisting toxilogical

1 data. This was mentioned before too. For many of the  
2 compounds, especially in the initial list, they are  
3 some of most highly test compounds on Earth, and  
4 there's a lot of very apical and animal-intensive tests  
5 that have already been done on these. All of this data  
6 should be considered before making a decision of  
7 whether or not a chemical needs to be tested. A more  
8 efficient approach would also contain an initial tier  
9 of completely non-animal mechanism-based assays. For  
10 example, QSARs and a broad spectrum of cell-based  
11 assays. This would also be consistent with NRCs  
12 recommendations for effective toxicity testing,  
13 referring to that NRC report that was issued last June  
14 I believe it was. And this would fulfill the intended  
15 purpose of the tier-1, which is to identify substances  
16 that have a potential to interact with the endocrine  
17 hormonal systems and would use many fewer animals,  
18 resources, and time. Such an approach is kind of  
19 familiar. It looks a lot like the OECD conceptual  
20 framework. Now I understand that the conceptual  
21 framework is not intended as a tier, but it does  
22 provide sort of a logical framework with which one  
23 could devise a more efficient process. And if you  
24 compare the EPA's EDSP tiers to the OECD conceptual  
25 framework, you'll see that the framework, the levels,

1 the early levels in the framework consist entirely of  
2 existing data, chemical properties, and an entire  
3 battery of broad spectrum in-vitro assays. I also  
4 realize that a lot of these are not yet validated.  
5 However, if one were to take a more logical approach to  
6 this, one would, I think, spend the resources, time,  
7 and effort designing something from the ground up  
8 rather than from the sides in. And then it's only in  
9 level three and level four that you get to the more  
10 extensive animal assays.

11           Okay. So in summary, really the EPA has yet  
12 to articulate what this vast catalog of data will be  
13 used for. This has also been mentioned previously.  
14 What is the human health issue that we're talking about  
15 here, and how will this data be applied to regulation?  
16 Will it have any effect on regulation of these  
17 compounds at all? We don't know that. It's far from  
18 clear that the EDSP will result in effective  
19 regulation. What is clear is that the design, the  
20 clinic design of the EDSP is based on expedience rather  
21 than some science, and right now as it stands is a  
22 waste of animal lives, if it proceeds as it is.

23           So I'm very heartened to hear that there will  
24 be a review and that the EDSP will be subject to  
25 modification change, updating, that sort of thing. I

1 very much encourage that to happen to keep up with  
2 modern science and what we've learned, and that's it  
3 for me. Any questions?

4 **DR. HEERINGA:** Thank you, Dr. Willet.  
5 Any questions for Dr. Willet on her presentation? Dr.  
6 Lasley?

7 **DR. LASLEY:** Lasley, UC Davis. To see if  
8 I understand you correctly, your proposing a system  
9 where information in the literature would be used as it  
10 is; is that right? I mean, that any published report  
11 on a chemical could then be used independent of its  
12 design or quality control. I mean, I don't understand  
13 how that would work.

14 **DR. WILLET:** Well what I'm saying is  
15 many of the compounds have already been tested in  
16 assays, for example, in a multi-generation assay  
17 development, especially the pesticides, and since  
18 they've already been in what would be considered  
19 actually higher than tier-1; if you already have that  
20 information, why do you need to go back and do a tier-1  
21 battery n that?

22 **DR. LASLEY:** I was stating to quality  
23 control.

24 **DR. WILLET:** Okay. I think you should  
25 use all appropriate data.



1 **DR. HEERINGA:** Additional questions from  
2 the panel? Thank you, Dr. Willet. At this point in  
3 our proceedings we have completed the period of public  
4 comment, and we are now at just short of 4:00 p.m.  
5 What I am proposing to do is to adjourn the meeting for  
6 today. We would move on to the charge questions, but I  
7 think there's merit in having everyone have a chance to  
8 absorb the information that they not only came prepared  
9 with but what we've heard today. And that should give  
10 Dr. Furlow some rest from his redeye flight from  
11 California via Vegas and Atlanta, right? That's the  
12 most unusual set of connections to unintentionally go  
13 to Las Vegas. In any case, so I'd like to adjourn for  
14 today, and we'll resume tomorrow morning, and it is  
15 scheduled for 9 o'clock on the agenda. I can't change  
16 that, so we will start at 9 o'clock tomorrow morning;  
17 and we'll open with some review comments from the EPA  
18 scientific staff, and then we'll move to the charge  
19 questions. So have a good evening everything, and  
20 we'll see you tomorrow morning at 9:00 a.m. Panel  
21 members, if we could just meet in the breakout room  
22 here briefly to discuss organization of our comments  
23 and writing assignments.  
24 (**WHEREUPON**, the meeting was adjourned at 3:58 p.m.)  
25

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SUBMITTED ON March 25, 2008



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